Medical Uses of Cortisone

Including Hydrocortisone and Corticotropin

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New York THE BLAKISTON COMPANY INC Toronto

Library of Congress Catalog Card No 54 9194

PRINTED IN THE UNITED STATES OF AMERICA
BY THE MAPLE PRESS COMPANY YORK PA

Dedication

This monograph is dedicated
by its authors
to
Dr E C Kendall
in appreciation of his fundamental contributions
to the development of cortisone

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Preface

Five years have passed since the anti inflammatory effect of cortisone was announced and since this hormone was made available to physicians During this period extensive investigations have been made of the action and uses of cortisone hydrocortisone and corticotropin Becau e of the wide spread interest in the effects of these hormones studies have tended to be scattered among the numerous medical specialties There is no compilation of these results and there is no authoritative compendium of sound clinical judgment concerning their use It is the purpose of this monograph to fill these needs

Accordingly the judgment of a group of physicians with wide experience in the use of adrenal hormone therapy has been assembled in one volume The authors not only cite the ample literature in their several fields but present their own conclusions as to the place of these hormones in various diseases Where there is agreement much repetition has been allowed in order to record these relatively new medical experiences as fully as possible With equal justification some differing and possibly contrary opinions have been retained The Editor has tried not to interfere with any author s freedom of expression except when limitations of space or the factor of unnecessary repetition demanded curtailment Consequently he accepts no credit for the accumulated wealth of knowledge here presented although he takes a collector s pride in the presentation of so many outstanding chapters Certainly profound thanks are due to the already overburdened authors who have taken the time to record and thus to share such valuable information Their reports should provide an excellent guide to the constructive employment of cortisone and related hormones in medicine The most effective and safe use of the e agents will demand of physicians a skill similar to that which they now apply to the use of such mainstays of medical practice as digitalis thyroxin and insulin

In addition the help of many friends is gratefully acknowledged Drs Robert F Loeb Dickinson W Richards Chester S Keefer Walter A Bauer Augustus Gibson and Charles E Lyght helped in the selection of the topics and the planning of the monograph Drs F Curtis Dohan Donald M Pillsbury William L Peltz P Robb McDonald Joseph L Hollander J Kapp Clark and William A Jeffers have helped by reading one or more chapters Particular thanks are due Miss Elizabeth Michel for her assistance in editing the manuscripts and in indexing this volume

E D W L

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Physiology of the Adrenal Cortex

Jane A Russell and Alfred E Wilhelmi

Although it is now nearly a hundred years since Addison first described the symptoms of adrenal insufficiency in man it is only in the past twenty five years that some understanding of the adrenal cortex as an organ of internal secretion has been gained Swingle and Pfiffner[1] and Hartman and Brownell[2] in 1930 were the first investigators to prepare extracts of adrenal cortex tissue which were active in maintaining life in adrenalectomized animals Since that time intensive physiologic studies of the actions of adrenocortical extracts have been accompanied by an even more arduous and thoroughgoing study of the chemistry of the adrenal cortex and the nature of its active principles Four groups of investigators led by T Reichstein in Switzerland and E C Kendall O Wintersteiner and J J Pfiffner in the United States have played a major part in the isolation and characterization of six active and more than twenty inactive crystalline steroids from the adrenal cortex [3] The first demonstration of the physiologic activity of a crystalline product of the adrenal gland was made in 1936 by Mason Myers and Kendall [4] who showed that compound E of their series (11-dehydro-17 hydroxycorticosterone later named cortisone by Kendall and Hench) could restore the vigor and endurance of the working muscle of the adrenalectomized rat Ten years later Sarett[5] reported the first partial synthesis of cortisone from ox bile by 1948 a commercially feasible process had been achieved by utilizing the discoveries of Kendall [6] Sarett [5b] and their associates Thus cortisone became available in quantities which permitted its applications in clinical medicine and greatly increased the range and depth of fundamental studies of adrenocortical function

The stimulus to this contemporary activity came about through the convergence of results of fundamental studies of adrenocortical function with the ideas developed by Hench and his colleagues[7] [8] during their clinical

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study of rheumatoid arthritis from 1923 to 1949 Their work gradually led them to the conviction that the processes of the disease were reversible and to the realization that the circumstances in which this reversibility was sometimes manifested—pregnancy jaundice foreign protein reactions starvation surgical operations and other stresses—were of such variety that the alleviation of symptoms could best be explained in terms of some common denominator a substance possibly a hormone, elaborated by the body In the latter years of this study other investigators had begun to define the metabolic actions of the adrenal cortex and were establishing the point by a multiplicity of observations, that in normal animals the secretory activity of the gland was increased in a wide variety of conditions of stress many of which were similar to those which Hench and his colleagues had learned to associate with the relief of rheumatoid arthritis This revived and strengthened an earlier view which had been laid aside for some years that the adrenal cortex might be associated with the disease At the first opportunity when cortisone became available in sufficient amounts in 1948 it was tried in a series of patients Early in 1949 an additional series of observations was made with cortisone and with corticotropin The excellent therapeutic effects of both these agents were reported by Hench et al [9] in April 1949 The fruit of these observations is attested in the remainder of this volume

Three points may be made in bringing this brief introduction to a close First the practical therapeutic applications of cortisone and corticotropin provide one of the most brilliant contemporary examples of the value of research directed toward the fundamental understanding of physical chemical physiologic and pathologic processes Second it illustrates the interdependence of scientific knowledge since the practical realization of a very good idea arising from a fundamental clinical investigation had to await the development of thought and practice in synthetic organic chemistry biochemistry and physiology as well as the development of industrial energies and skills of a very uncommon order Finally a legitimate pride in practical achievement must be moderated by the fact that the fundamental problem is as yet unsolved the essential mechanism of action of the adrenocortical hormones is not understood

The Adrenal Gland

The mammalian adrenal gland is a compound endocrine organ consisting of a thick cellular cortex secreting the cortical hormones and a medullary portion which secretes the hormones epinephrine and norepinephrine The circulation to the two parts is common The entering vessels consisting usually of several branches from nearby arterial trunks, penetrate the capsule and then branch into arterioles and capillaries which pass toward the center of the gland The blood from these capillaries drains into sinusoidal spaces in the inner cortex and medulla and finally emerges from the gland in a single adrenal vein In embryonic origin the two parts of the adrenal gland are quite distinct the cortex arises from the celomic mesoderm

near the urogenital ridge and the medulla differentiates from the neural crest The nature of the secretions and the physiologic functions of the two parts are entirely different and although it seems unlikely that the intimate anatomic relationship found in higher animals should be irrational, no direct physiologic connection between them is now known

Structure

The adrenal gland varies in shape in different species from the nearly round organ seen in rodents to the flattened caplike structure found in man It is enclosed by a fairly heavy fibrous capsule which may penetrate the gland to some extent Within the capsule the large epithelioid cells of the cortex are arranged in loose cords or nets Three zones generally are distinguishable the zona glomerulosa a thin layer just beneath the capsule in which the cells are arranged in irregular layers the zona fasciculata the widest portion in which the cells are found in cords tending radially and the zona reticularis where the cells lie in loose anastomosing nets or whorls Histologic evidence suggests that the cells of the cortex arise primarily in the layers just beneath the capsule and move inward dividing and perhaps differentiating further as they do so and then finally degenerate and disappear in the reticular zone Although this view has been debated it is clear that after enucleation of the gland the remaining cells of the glomerulosa or capsule are capable of giving rise to all of the cells of the adrenal cortex [10] Also when bits of the adrenal capsule and glomerulosa are transplanted functioning glandular tissue develops but transplants containing only fascicular and reticular cells do not take [11] Thus if any differences in function of the several zones exist they would not appear to result from the presence of distinct strains of cells but most probably would depend upon the stages of maturity achieved by the cells in the different zones

In the human embryo the adrenal gland contains between the cortex proper and the medulla a thick boundary zone which has been described as the X zone or as the fetal cortex During late prenatal and early postnatal life this zone disappears by involution and is not observed again A somewhat similar distinctive zone has been described in the adrenal of the mouse here it appears shortly after birth and disappears some weeks later From indirect evidence this zone has been suspected of having an androgenic function [12] Whether the human fetal adrenal has any similar physiologic relationships is not known [13]

Chemistry The cells of the adrenal cortex are rich in lipids of several types In addition to much sudanophil material they contain also a large number of droplets both coarse and fine which are acetone soluble birefringent autofluorescent Schiff positive and reactive with hydrazines These properties collectively have been taken to indicate the presence of ketosteroids in the droplets since this is said to be the only group of compounds known which is characterized by all of these reactions [14 15] However it is quite possible that each of a number of different substances could display some of the reactions and the identification of ketosteroids by these

procedures has been disputed Since the most specific of these reactions the formation of hydrazones occurs with steroids containing ketone groups at carbon 3 17 or 20 [16] it is obvious that at best these histochemical methods cannot differentiate between physiologically active and inactive steroids in the gland The distributions of the sudanophil material and of the "ketosteroids have received much attention as possible indicators of physiologic activity in different regions of the gland [15,17,18] Normally there are moderate amounts of these substances in the glomerular zone little if any in a thin band separating the glomerular and fascicular zones (called the sudanophobe zone) and fairly intense reactions in the fasciculata, especially in the outer half or two thirds of this region Diminution in the amount of visible lipids, in particular the ketosteroids," may be associated with either decreased or increased function

Cholesterol is found in the adrenal in very high concentrations (up to 4 or 5 per cent of the wet weight), and a considerable part of the sudanophilia and birefringence of the cortex must result from the presence of this substance In contrast to other tissues in which cholesterol is a relatively unvarying constituent the adrenal may exhibit very marked fluctuations in its cholesterol content in different physiologic conditions In general, the cholesterol level is high when the gland is inactive and is depleted when it is stimulated to secrete the adrenal hormone [18,19]

Another conspicuous component of adrenocortical tissue is ascorbic acid Extensive investigations of the adrenals of rodents have indicated that this substance undergoes depletion whenever the adrenals are stimulated by either endogenous or exogenous adrenocorticotropic hormone [20]

Control by the Anterior Pituitary

The adrenal cortex is nearly completely dependent for its functional integrity upon activation by the adrenocorticotropic principle from the anterior pituitary [21-24] Not only is corticotropin essential for the maintenance of the normal size and architecture of the gland, but its continual secretion is required to stimulate the adrenal cortex to respond to the varying needs of the animal

As P E Smith first demonstrated in 1916, removal of the hypophysis is followed by marked atrophy of the adrenal cortex In rodents the weight of the adrenal a few weeks after hypophysectomy is about one-half or one-third of the normal but in other species the decrease in size may not be so marked The cells of the cortex are diminished both in size and in number and though they remain viable in appearance they are largely depleted of the stainable lipid and ketosteroid" droplets which are normally found [24] The large fascicular zone is most affected frequently being reduced to only a fraction of its normal width The glomerular zone usually exhibits little change in size In the rat this zone retains the usual lipid and ' ketosteroid' reactions but in other species these cells too may be depleted of lipid [3,24]

Functionally the hypophysectomized animal exhibits most of the changes shown by adrenalectomized animals except that usually it does not die of the adrenal deficiency The effects of adrenalectomy upon diabetes

mellitus, muscle function, mesenchymal tissue changes and sensitivity to stress of all types are practically duplicated by hypophysectomy. However, the hypophysectomized animal in ordinary circumstances can maintain nearly normal concentrations of salts in its body fluids. For this reason and because of the apparent autonomous existence of the glomerular zone of the adrenal cortex, it has been proposed that the salt and water functions of the adrenal cortex are not under pituitary regulation and that the glomerular region is the site of secretion of the steroids responsible for this function.[15,21] Additional evidence for this theory has been presented by Deane, Shaw and Greep[18] who described histochemical changes induced in the glomerulosa by alterations in the salt content of the diet or by administration of desoxycorticosterone (DOC). However, this view has not yet been found universally acceptable.[23,4] The administration of corticotropin is not without effect upon salt and water balances or upon the histochemistry of the glomerulosa;[5,26] moreover, secretion of a specific salt and water hormone has not yet been demonstrated. As will be noted later, minute amounts of some of the adrenal steroids, amounts far from adequate for normal function in most respects, still are capable of maintaining life in adrenalectomized animals. Such a basal secretion might well continue from the adrenals of the hypophysectomized animal, either from the glomerulosa or perhaps from the remaining fascicular cells.

The rather remarkable powers of regeneration and of physiologic hypertrophy of the adrenal cortex are completely dependent upon the presence of the pituitary. When the adrenal glands are enucleated and only a small part of the glomerulosa left adherent to the capsule, complete regeneration of the cortex occurs within a short time, and similarly the removal of one adrenal is followed by hypertrophy, but neither of these processes occurs at all in the absence of the hypophysis, nor does enlargement of the adrenals occur with continued stresses of various types. The evidence on this point has been discussed fully by several investigators.[2-4,7]

The action of corticotropin, either endogenous or exogenous, apparently is first to stimulate the formation and immediate secretion of cortical hormone, for chemical changes in the gland and effects of increased secretion are readily detected within an hour or less. One of these effects, the rapid depletion of ascorbic acid in the adrenal cortex, has been widely employed as an indicator of the secretion of corticotropin by the pituitary and in the assay of corticotropin preparations. Other changes include the depletion of the cholesterol content of the gland and diminution or disappearance of the staining reactions for lipids and for ketosteroids. On continued stimulation of the cortex by corticotropin, if it is not too severe, these materials may reappear and persist or even be increased in amount during the subsequent period of growth of the gland. With prolonged extreme stimulation the cortex becomes greatly enlarged but may be nearly empty of ketosteroids; subsequently areas of hemorrhagic necrosis and fatty infiltration may appear in the inner zones. This stage has been described frequently as one of exhaustion, but this is not certainly the case.[3,24,7]

The means by which corticotropin effects its control of cortical activity

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as λ is then seldom less than 0.15 or 0.20 corresponding roughly to an error of ±40 to 60 per cent When the e activities are compared to those of the respective standard preparations and a ratio is then made between two such relative potencies (as in the ratio ascorbic acid activity adrenal weight activity) the standard error of this ratio is at least 0.3 log units corresponding to a range of from one half to two times or fourfold The 95 per cent confidence limits here would be about 0.6 log units or a range of sixteenfold Obviously, unless complete assays with full statistical treatment are performed only very large differences in potency ratios may be considered significant

Second the ratio of potencies obtained in different methods of assay need not agree if the mechanics of the respon e are essentially different For instance a response related to a single pul e of enhanced secretory activity may be essentially independent of any duration of effect whereas a response related to su tained activity and growth may be not only dependent upon duration of effect but limited in rate and magnitude by the very nature of the cellular processes that are being stimulated In the latter case the physical and chemical properties of different active preparations may be instrumental in determining the proportion of a dose lost by inactiva tion or excretion the rate of access of active material to the target and the duration of effect in the target organ itself Until some means of critical examination of these possibilities is devised it will not be possible to draw any certain conclusions from discrepancies in potency ratios between different methods of bioassay

The Adrenal Steroids

Chemistry and Properties

Of the 28 known crystalline steroid isolated from the adrenal cortex only the 6 illustrated in Figure 1 have so far been found to have marked characteristic biologic activity [8, 35] They are all C-21 oxysteroids The com mon features essential to their biologic actions are the $\alpha\beta$ unsaturated 3 ketone grouping in ring A and the α ketol side chain at carbon 17 oriented on the same side of the plane of the ring as the angular methyl groups at C-10 and C-13 The ab ence of an oxygen atom at C 11 as in 11 desoxy-corticosterone (DOC) and 11 desoxy 17 hydroxycorticosterone (compound S or 11 desoxycortisone) is associated with virtual ab ence of effects upon carbohydrate metabolism but with most marked effects upon electrolytes and water The four compounds with a ketone or hydroxyl group at C-11 are less active with respect to electrolytes and water and are highly active in carbohydrate metabolism The latter activity is greater in those com pounds with a 17 hydroxy substituent and is greatest in 17 hydroxycorti costerone (hydrocortisone) in which there is an 11 hydroxy group as well

The inactive (or very much less active) steroids isolated from the adrenal cortex differ from this group in one or more of the following respects (1) Ring A is saturated and the 3 ketone group is reduced to a hydroxyl group

is unknown Since the amounts of hormone present in the adrenal are small relative to the amounts secreted under the influence of corticotropin it seems likely that a part at least of the action of corticotropin should be on some phase of the synthesis of the steroids peculiar to this organ This has also been indicated to be the case by the recent observation that corticotropin increased the uptake of C^{14} from acetate into 17 hydroxycorticosterone (compound F or hydrocortisone) by adrenal tissue *in vitro*[28] The depletion of cholesterol in the gland may readily be envisioned as a result of its conversion to adrenal hormone the changes in "ketosteroids," which may include intermediate products as well as hormonal steroids may be interpreted similarly The meaning of the depletion of ascorbic acid is obscure for other evidence of adrenal activity may be seen in scorbutic guinea pigs or in avian species in which the ascorbic acid does not appear to be affected It seems possible that subsequent hypertrophy of the cortex is a consequence of the continued activity of the cells in producing the hormone under the influence of corticotropin

Adrenocorticotropic Hormone

The preparation properties bioassay of corticotropin, and control of its secretion are described in the following chapter in connection with the use of this hormone in man Among these important categories one current laboratory problem deserves comment Various protein and polypeptide fractions which have physiologic activity have been prepared This fragmentation of corticotropin has brought with it the question of the fragmentation of its biologic effects as well More than one worker[29-32] has observed that different preparations of corticotropin may differ widely from one another and from the standard protein preparation in the ratio of their activities in the ascorbic acid depletion test[33] and in the adrenal repair test[29 33 34] Because a number of investigators have found no correlation between the potency of certain nonprotein corticotropin preparations in the Sayers test[33] and in adrenal weight-repair or -maintenance tests it has been suggested that there may be an adrenal weight-increasing factor and an ascorbic acid-depleting factor which are partly separated from one another in the newer methods of purifying corticotropin[30 32] As yet these two activities have not been completely separated and although the possibility of more than one factor cannot be excluded the following points must be kept in mind First all of the methods of assay of corticotropin even when conducted in proper design with adequate numbers of animals are subject to errors of the order of at least 25 per cent Not many published estimates of the potency of corticotropin preparations have actually been established by full dress assay and they are therefore subject to much larger errors

From published data the standard deviation of these assays by either the adrenal weight or ascorbic acid-depletion methods may be calculated to be in most cases of the order of 0 4 to 0 5 in terms of logarithm of the dosage[34] With small groups of animals, the standard error of a single group

The α ketol side chain is capable of reducing alkaline silver diamine triphenyltetrazolium chloride alkaline copper and phosphomolybdic acid The last two reactions have been standardized and applied to the quantitative determination of small amounts of compounds of this type [37, 38] The α β unsaturated 3 ketone grouping also reduces phosphomolybdic acid so that compounds containing either or both of these groupings are determined by this reagent When a 17 hydroxy group is present with the α ketol side chain, reaction with 2 4 dinitrophenylhydrazine leads to the formation of an osazone This reaction has been applied to the quantitative determination of cortisone by Porter and Silber [39] and to the determination of blood corticosteroids in the method of Nelson and Samuels [40] The oxidation with chromic oxide of 17 hydroxy compounds with α ketol or glycol side chains yields 17 ketosteroids and this reaction has been applied to the estimation of this class of compounds in urine by determining 17 ketosteroids before and after oxidation [41] Periodic acid oxidation yields formaldehyde from compounds possessing either the α ketol or the glycol side chain [42] This reaction forms the basis of the estimation of the formaldehydogenic steroids in urine extracts [43–45] Compounds with an oxygen function at C-11 tend to lose water in acid solution forming a 9 11 unsaturated steroid Derivatives of this type have been identified in urine extracts [46, 47]

The 28 crystalline steroids isolated from adrenocortical extracts do not represent the sum of the biologic activity of the crude extracts Whatever the method of fractionation employed a noncrystalline residue remains—the so called amorphous fraction—which contains from 10 to 50 per cent of the total activity as judged by life maintenance of the original crude extract Although the solubility properties and apparent chemical composition of the amorphous fraction resemble those of the $C_{21}O$ steroids its biologic actions are more like those of DOC No systematic study of the biologic effects of this fraction has yet been made since only limited amounts have been available Ingle [48] in a review of a number of reports has suggested that the observed effects and the order of activity are sufficiently at variance with those of the known active compounds to indicate that new products with hitherto unrecognized types of biologic action may yet be isolated from the amorphous fraction

The first partial synthesis of an active corticosteroid DOC was achieved by Steiger and Reichstein[49] in 1937 and for some time this was the only adrenal steroid available in any appreciable quantities Although it is most active in life maintenance DOC does not have many of the effects of adrenocortical extracts which are now associated with the 11 oxysteroids Since the natural sources of the 11 oxysteroids of adrenal origin are limited a great effort much intensified by the demonstration in 1949[7] of the therapeutic effects of cortisone has been exerted in the synthesis of these compounds The major problems were (1) the selection of cheap abundant and appropriate starting materials for partial synthesis (2) devising methods for the introduction of oxygen at C 11 and (3) the construction of the dihydroxyacetone grouping correctly oriented at C 17 There is at present

(2) The 20-ketone group is reduced so that the side chain becomes a glycol CH OH CHOH– (3) The 21 alcohol group is reduced to a methyl group (4) The side chain is lost leaving a ketone group at C-17 Various combinations of these four changes can lead to a large number of inactive steroids sharing some of the chemical and physical properties of the six active substances This has contributed to the difficulties of their isolation

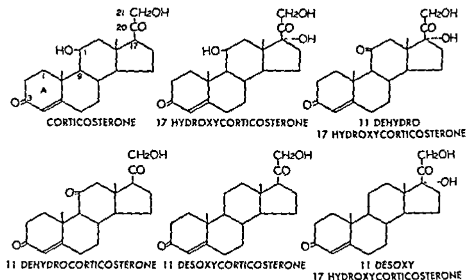


FIG 1 *Structure of the six known active adrenal steroids* The parent saturated hydrocarbon of the C 21 steroids is allopregnane By convention the angular methyl groups at C 10 and C 13 lie on the same side of the plane of the ring system projecting above the plane of the paper The spatial relation of substituents in the nucleus e g the 11 or 17 hydroxy groups is designated β if they are on the same side of the plane of the rings as the angular methyl groups α if their projection is opposite The orientation of the side chain at C 17 has been shown to be β the 17 hydroxy group therefore has the α-orientation The designations given the compounds by different investigators are as follows Corticosterone—Kendall's B Reichstein's H 17 Hydroxycorticosterone—Kendall's F Reichstein's M hydrocortisone 11 Dehydro 17 hydroxycorticosterone—Kendall's E Reichstein's Fa Wintersteiner's F cortisone 11 Dehydrocorticosterone—Kendall's A 11 Desoxycorticosterone—Reichstein's Q DOC 11 Desoxy 17 hydroxycorticosterone—Reichstein's S 11-desoxycortisone

and identification as well as to the uncertainty and lack of specificity of methods for their determination in urine blood and tissues

The loss of the side chain may lead to a series of C-19 steroids with androgenic activity of which three have actually been isolated in crystalline form androstane 3β 11β diol 17 one Δ^4 androstene-3 11 17 trione (adrenosterone) and Δ^4 androstene 3 17 dione Whether these represent products of a normal functional activity of the adrenal cortex by products or intermediates in the synthesis or metabolism of the C 21 steroids products of abnormal cortical metabolism or artifacts of the processes of extraction and isolation cannot be decided certainly A thorough and systematic study of the androgenic substances of the adrenal cortex has yet to be made [26]

of these compounds from cholesterol or some other precursor Perfusions with either acetate or cholesterol tagged with C^{14} led to the production of radioactive adrenal steroids so that both compounds may serve as precursors

The results of studies of the synthetic activities of minces of hog adrenals incubated *in vitro* by Haines[60] confirm in many respects the observations made by perfusion Incubation of aerated hog adrenal breis for 48 to 120 hours brings about a large increase in active steroid content as judged by assays by the Ingle muscle work test or by the glycogen deposition test cited later in this chapter It was found incidentally that quick frozen glands contained more than twice as much carbohydrate regulating hormone activity as glands collected without immediate freezing and that a large proportion of the activity was lost during a few hours autolysis In the presence of added substrates— DOC and 11 desoxycortisone— the hog gland brei like the perfused adrenal produces the corresponding 11 hydroxy compounds This procedure expanded to large scale may therefore greatly augment the supplies of corticosterone and hydrocortisone When radioactive acetate is used as a substrate the brei synthesizes a mixture of radio active adrenal steroids predominantly however hydrocortisone— which accounts for over 90 per cent of the measurable carbohydrate-regulating activity

Similar observations have been made by others working with adrenal tissue slices or homogenates The picture of the intermediate transformations giving rise to the adrenal steroids is of course far from complete Although acetate is a known precursor of cholesterol as well as a precursor of the adrenal steroids it is probable but not certainly established that cholesterol is not an obligatory intermediate in the latter synthesis The ease with which DOC is 11 hydroxylated does not imply that it is a normal intermediate in the synthetic process since neither it nor corticosterone appears to undergo any further change on long term incubation or perfusion and yet most workers are agreed that hydrocortisone is always predominant in the mixture of steroids found in the freshest glands and in the mixture formed during synthesis from acetate or cholesterol

Some of the implications of the foregoing studies are borne out by the observations of investigators who have succeeded in measuring and identifying adrenal steroids in blood[55,61–63] In every instance the corticosteroid present in largest amount (in peripheral vein blood or adrenal vein blood after injection of corticotropin in dogs) was hydrocortisone Corticosterone was usually also present but in much smaller amounts Nelson et al[64] using a method specific for 17 hydroxycorticosteroids[48] found 4 to 10 micrograms of such material (which may be presumed to be mainly hydrocortisone) per 100 cc of peripheral blood of human subjects The amounts were increased after injection of corticotropin and it is interesting to note that their best sustained effects with lower dosages were obtained with constant intravenous infusion of corticotropin

no complete account of the successful efforts of many groups of workers who have dealt with these problems indeed the present intensity of work and the rate of discovery of new and improved procedures nearly preclude a comprehensive review at this time Partial accounts of the work are presented by Heard [35] Kendall [6] and Julian [50] The more recent phases of the work are the development of methods for using soya steroids and steroidal sapogenins in addition to the bile acids (a more limited source) as starting materials [51] the devising of methods of total synthesis by Woodward[52] and Sarett [53] and their associates and the discovery that certain microorganisms can introduce oxygen at C-11 into the relatively more easily synthesized DOC and 11 desoxycortisone [54]

Formation and Secretion

Knowledge of the biosynthesis of the adrenal steroids and of the nature of the compounds secreted by the gland has recently been extended by the study of isolated perfused surviving adrenal glands by successful incubations of adrenal gland minces and by application of micromethods for the determination of blood corticosteroids The success of these investigations depends upon recent technical developments in methods of column chromatography in infrared spectrophotometry and most recently in the method of paper chromatography devised by Zaffaroni and his associates[55-7] which makes possible the separation identification and semiquantitative determination of microgram quantities of the adrenal steroids

Perfusions of isolated beef adrenals by Hechter and associates[58] and by Zaffaroni Hechter and Pincus[59] have thrown much light on the nature of synthetic and secretory processes in the gland The untreated adrenals release small variable but significant amounts of formaldehydogenic steroids into the perfusate The output is greatly increased when corticotropin is added to the medium and this is the result of increased synthesis rather than increased liberation since the total amount of steroids in the system greatly increases Although 15 different α ketols may be detected in the perfusates 60 per cent of the total is accounted for by corticosterone and hydrocortisone the amounts of all the α ketols are however increased in about the same proportion when corticotropin is added Addition to the perfusate of DOC 11 desoxycortisone Δ^4 androstene 3 17 dione androsterone and progesterone led to the appearance of the corresponding 11β hydroxy compounds The glands appeared to be unable to introduce a 17 hydroxy group into DOC or into corticosterone but with added progesterone 17 hydroxyprogesterone and pregnenolone the products found were 11 hydroxyprogesterone 17 hydroxyprogesterone corticosterone and hydrocortisone The gland therefore can introduce a hydroxyl group at C-11 C-17 and C 21 and can also alter the 3β hydroxyl (of pregnenolone) to an $\alpha\beta$ unsaturated 3 ketone Since these transformations occur readily in the absence of corticotropin it is suggested that the action of corticotropin in promoting synthesis must be on some earlier stage in the formation

of these compounds from cholesterol or some other precursor Perfusions with either acetate or cholesterol tagged with C^{14} led to the production of radioactive adrenal steroids so that both compounds may serve as precursors

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Excretion

Three general types of method have been applied to the study of urinary adrenal steroids and their derivatives bioassay, chemical determination, and isolation and identification Each method suffers from the limitation that the amounts of these materials are very small, not only presenting difficulties in suitable extraction and estimation but also constituting a meager fraction a wavering and possibly unfaithful reflection of the total adrenocortical secretion The methods must also compromise with two complicating circumstances The first is lack of specificity No bioassay tells which active compounds might be present, and the several chemical methods measure functions which are possessed not only by the active adrenal steroids but also by their less active derivatives and by many other components of extracts of urinary lipids The second complication lies in the fact that many of these substances are excreted as conjugates with glucuronic or sulfuric acid They are not all equally sensitive to the same methods of hydrolysis and many of them undergo chemical change in the process

Extracts of urine have been assayed in adrenalectomized animals for various characteristic effects – life maintenance resistance to insulin or to water intoxication work performance protection from cold and deposition of liver glycogen during fasting The latter two form the basis of several *sensitive and reasonably accurate bioassays for the active (11 oxy) cortico* steroids –the glucocorticoids—in urine [24, 65] which have been widely used in clinical studies [66]

The chemical properties responsible for the action of the adrenal steroids in reducing phosphomolybdic acid or alkaline copper or in generating formaldehyde on oxidation with periodic acid or 17 ketosteroids on oxidation with chromic oxide have already been outlined The methods based on these properties are convenient and useful but they measure broad classes of compounds and are subject to large errors [24, 67] One fairly simple and accurate chemical determination which has been widely employed is the estimation of 17 ketosteroids [67, 68] It is now generally agreed that about one third of the daily excretion of these compounds in the male takes origin from the testis the remainder is derived from the adrenal cortex which also appears to be wholly responsible for the excretion of 17 ketosteroids in the female The origin of these compounds is still in some doubt They may arise from the adrenal androgens if androgens are in fact products of the normal adrenal cortex The ease with which the 17 hydroxy α ketols or glycols may lose their side chain on mild oxidation suggests that the 17 ketosteroids may be derived from this group of the adrenal steroids This is borne out by the recent observation that the administration of cortisone is followed by a small but significant rise in 17 ketosteroid excretion by the isolation from urine extracts of 11 oxy-17 ketosteroids and by the observation that the administration of DOC corticosterone or progesterone, which are lacking the 17 hydroxy group does not lead to a rise in 17 ketosteroids Although the administration of corticotropin has

been shown to increase the excretion of glucocorticoids formaldehydogenic or reducing steroids and 17 ketosteroids alike not every condition in which there is evidence of increased adrenocortical activity is accompanied by a rise in 17 ketosteroids Conversely there are circumstances mainly instances of tumors of the adrenal cortex, in which the 17 ketosteroids alone are greatly increased Because of this lack of correspondence some investigators have concluded that the 17 ketosteroids are indicators of an aspect of adrenocortical activity (for instance a supposed androgenic function) different from that giving rise to the glucocorticoids and the reducing and formaldehydogenic steroids It must be remembered, however that the urinary steroids represent only a fraction of the total secretion and that the mixture of compounds excreted is a resultant of the composition of the output of the adrenal cortex (normal and abnormal) and of the changes in this composition brought about by the (normal or abnormal) metabolism of the corticosteroids in the tissues Until more is known about the metabolic fate of the adrenocortical hormones in different organs and in different circumstances the 17 ketosteroids must be a rather uncertain index of adrenocortical activity

Table 1 presents a limited sample of representative values for the urinary corticosteroids as determined by the various available methods More extensive data may be found in papers by Sayers [4] and Venning[66] and for 17 ketosteroids by Dorfman[36] and Mason and Engstrom [63] The points of greatest interest are the small amounts excreted daily by normal persons and the relative orders of magnitude of the glucocorticoids the reducing and formaldehydogenic steroids and the 17 ketosteroids

Table 1

MILLIGRAMS OF URINARY CORTICOSTEROIDS EXCRETED IN TWENTY FOUR HOURS AS DETERMINED BY DIFFERENT METHODS

Subjects	*Glucocorticoids*	*Formaldehydogenic Steroids*	*Reducing Steroids*		*17 Ketosteroids*
			Copper	*Phosphomolybdate*	
Normal Males	0 04–0 09	0 5–1 7	0 10–0 40	1 0–2 [illegible]	5–30
Normal Females	0 03–0 07	0 4–1 1	0 10–0 40	1 0–2 0	2–22
Cushing s Syndrome	0 04–0 70	0 8–23 0	0 90–12 0	4 8	20–800
Addison s Disease	0 00–0 015	0 1–0 8	0 02–0 [illegible]6		0 0–7 5

* Reckoned as cortisone

The isolation and identification of urinary steroids have provided a great deal of information about the nature of steroid metabolites and about the possible pathways of change which the steroid hormones may follow in the body [35 36 46 57] More than 50 pure steroids have by now been isolated and characterized and the possibilities of finding additional new members of the

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Extracts of urine have been assayed in adrenalectomized animals for various characteristic effects – life maintenance, resistance to insulin or to water intoxication, work performance, protection from cold, and deposition of liver glycogen during fasting. The latter two form the basis of several sensitive and reasonably accurate bioassays for the active (11-oxy-) corticosteroids — the glucocorticoids — in urine,[24, 65] which have been widely used in clinical studies.[66]

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once the critical postoperative period was passed The removal of the adrenal medullas alone was shown not to endanger life

After the removal of the adrenal glands a variety of metabolic defects become evident[75-77] At first if operative shock has been avoided the animal appears relatively normal, but later a decline sets in rather abruptly in some cases and death occurs in most species within a few weeks The symptoms seen before death include anorexia asthenia vomiting and diarrhea hypoglycemia hypotension, hemoconcentration, often a fall in body temperature and renal failure In young animals growth ceases in older animals there is usually loss of weight The adrenalectomized animal is also extremely susceptible to stresses of all types such as trauma cold heat or infection The cause of death varies Shock with hemoconcentration and renal failure is perhaps the most frequent cause but in some species like the rat, hypoglycemia may be fatal before the full course of the other defects is run Death from infection or other stress is common in all species

Biochemical Changes

The biochemical changes associated with adrenocortical deficiency concern chiefly the concentrations of electrolytes and water in the plasma and in the tissues and the metabolism of carbohydrates and protein

Electrolytes and Water Low concentrations of sodium and chloride ions in the plasma of adrenalectomized animals and beneficial effects of extra salt were first observed by Baumann in 1927 Some years later Loeb[78,79] observed similar changes in the plasma of patients with Addison s disease He also found that restriction of the salt intake could precipitate a crisis of adrenal insufficiency Since that time it has been well established that in the absence of the adrenals there is excessive excretion of sodium and chloride by the kidney and diminished clearance of potassium[80-84] In consequence the serum sodium falls and the serum potassium rises These changes are accompanied by movement of water and potassium into the cells (Table 2) and diminution in the extracellular fluid volume[85,86] The blood pressure then begins to fall the blood becomes more concentrated circulation time is increased and as a result the renal glomerular filtration rate is progressively diminished[87] The elevation of the blood nonprotein nitrogen (N P N) which is often seen is probably a consequence of the renal failure, since it develops somewhat later than the first hemodynamic defects and is prevented by treatment with saline (Tables 2 and 3)

Salt Therapy If sufficient amounts of sodium chloride with water are given to adrenalectomized animals the downward course may be slowed or prevented entirely The salt which continues to be lost in the urine is replaced by this treatment, and in addition the resulting diuresis helps to wash out the potassium which otherwise tends to accumulate (Tables 2 and 3) Hemoconcentration is prevented normal blood pressure and renal function may be maintained and appetite and digestion are improved Young adrenalectomized rats given 1 per cent salt in their drinking water

complex mixture of excretion products have not been exhausted A point of great interest is that the known active corticosteroids are rarely excreted unchanged in any very large amounts, even in conditions in which fairly large doses have been given or when the adrenal cortex has been powerfully stimulated This is borne out by the low values usually found for glucocorticoids (Table 1) Mason and Sprague[69] were the first to isolate an active corticosteroid hydrocortisone from the urine of a patient with Cushing's syndrome Later Mason[70] isolated cortisone from the urine of patients with Addison's disease or rheumatoid arthritis who had been treated with the hormone More recently Burton Zaffaroni and Keutmann[57] and Schneider[71] have identified small amounts of cortisone and hydrocortisone (of the order of 20 to 60 micrograms per liter) in the urine of normal persons No investigator has as yet found DOC in urine extracts

The steroid metabolites found in urine are generally more reduced than their presumed precursors The α β unsaturated 3 ketone grouping may be partly or completely reduced the oxygen at C-11 may be lost the α ketol side chain may be reduced in varying degrees or lost to leave a 17 ketosteroid These compounds tend to differ from the active corticosteroids therefore in much the same respects as the 22 companion steroids isolated from adrenal extracts This often makes it impossible to assign a definite origin to a given metabolite but certain structural signs—the presence of oxygen at C 11 (or of 9 11 unsaturation) in a few 17 ketosteroids and the presence of the side chain unchanged or partly reduced are clues to the origin of some of the metabolites from the adrenal The absence of certain metabolites from the urine in Addison's disease or their disappearance after adrenalectomy or castration and the appearance of some urinary steroids in large amounts in some instances of adrenocortical tumors have also provided clues to their origin An excellent account both of the progress made and of the difficulties to be met is given by Dobriner and Lieberman[46] New and improved analytical methods now make it possible to study the metabolism of the adrenal corticosteroids in isolated tissues Work of this kind should provide more direct information about the metabolites of the active cortical hormones The metabolic reduction of the α,β unsaturated 3 ketone grouping of cortisone and DOC by liver tissue *in vitro*, and the appearance of the products formed among the urinary steroids has already been reported by Schneider and Horstmann[7, 73]

Adrenal Insufficiency

That the adrenocortical secretion is essential for life or practically so was demonstrated by several investigators during the years 1920 to 1930[74, 75] Earlier disagreement as to the importance of this hormone was shown to be the result on the one hand of the great susceptibility of adrenalectomized animals to shock and sepsis which were often immediately fatal and on the other hand of the ability of cortical remnants or of extra adrenocortical "rests" to hypertrophy to the point of maintaining the animal indefinitely

may of itself result in low absorption rates, and adrenalectomized rats in which appetite and food intake have been well maintained by adequate salt treatment may exhibit normal rates of absorption. Hence it may be concluded that this deficiency is secondary to the diminished food intake and that it is not necessarily related directly to adrenocortical function. Indirect effects of adrenal deficiency include besides anorexia and digestive disturbances, loss of weight and of body fat, failure of young animals to grow, hemoconcentration, diminished renal plasma flow, defective glomerular filtration rates, and rise in blood N P N.

Table 3

KIDNEY FUNCTION IN THE ADRENALECTOMIZED DOG

	Clearances of		Ratio of K Urine Plasma	N P N Mg per 100 ml of plasma
	Creatinine Ml per minute	*Urea* Ml per minute		
Normal	58	33	28	16
Adrenalectomized untreated	21	8	10	72
Adrenalectomized given sodium salts	37	25	6	32
Adrenalectomized given cortical extract with salts	45	30	29	15

* All estimations were made on the same animal; each figure is the average of five determinations.

This table is based upon data contained in the article of Harrison and Darrow [83]

Although treatment with saline overcomes the loss of salt and prevents the disturbances in hemodynamics, the tubular reabsorption of sodium continues to be deficient and potassium is not concentrated normally in the urine [83, 84] These defects are corrected by treatment with cortical extracts or with certain adrenal steroids (Table 3).

Water Excretion. Another deficiency in adrenalectomized animals related possibly to the excretion of electrolytes but as yet incompletely understood is their failure to excrete excess water loads [90] This defect is shown by animals or human subjects with even a mild degree of insufficiency and it has been employed as the basis of a clinical test for Addison's disease. Several factors may contribute to the defect in water diuresis. One is that in subjects with low concentrations of salt in the extracellular fluids and increased osmolar concentrations intracellularly, a larger proportion of the ingested water would be expected to be taken into the cells, and this has in fact been demonstrated to be the case [91] However there is also retention of water in the extracellular compartment, so that this extrarenal disturbance cannot account for all of the deficiency. The diminution in renal plasma flow and in glomerular filtration rate also may contribute to the picture, but the latter disturbance may be largely controlled by administra-

are able to live indefinitely and to grow at nearly normal rates. The balance between the sodium and potassium ingested, as well as the amount of sodium, appears to be important, for excess potassium is deleterious and *in some species reduction in potassium intake as well as increase in sodium* is required for maintenance. Since adrenalectomized animals may be kept alive for prolonged or indefinite periods by control of the amounts of salts taken in, or even by peritoneal lavage,[88] cortical function cannot to this extent be said to be absolutely essential for life. However, the salt treated adrenalectomized animal is by no means restored entirely to normal and as will be seen, some of the remaining defects also are such as often to endanger life.

Table 2

PLASMA AND TISSUE ELECTROLYTES IN ADRENALECTOMIZED RATS

	Serum				Muscle	
	Na mEq per liter	*K* mEq per liter	*Cl* mEq per liter	*NPN* Mg per 100 cc	*Na* mEq per Kg of fat free tissue	*K* mEq per kg of fat free tissue
Normal	144	5.2	105	35	23.6	109
Adrenalectomized, untreated	136	7.4	97	96	18.8	117
Adrenalectomized, given sodium salts	143	5.7	102	28	23.6	109
Adrenalectomized, given cortical extract for 48 hours	143	5.5	101	22	21.0	106

* All the adrenalectomized rats were allowed to become insufficient before treatment was started with sodium salts (chloride and bicarbonate) or cortical extract. The figures are averages from groups of 8 to 20 rats.

This table is based upon data contained in the article of Harrison and Darrow.[85]

The fact that some of the more prominent effects of adrenal insufficiency may be treated successfully by other means than substitution of the hormone has two consequences which are important in any consideration of adrenal physiology. One is that since under certain conditions no hormone at all may be required to maintain a semblance of normality, the amount of hormone needed by the deficient subject will vary very greatly depending upon the diet and other conditions and also upon the criteria chosen.[89] Hence also wide variations may be manifest in the apparent potencies of cortical preparations.

The second consequence of the success of treatment with salt or similar therapy is that it allows a distinction to be drawn between what have been called direct and indirect effects of adrenal insufficiency. For example, a low rate of absorption of glucose from the gastrointestinal tract has been reported frequently in adrenalectomized rats. However, in normal rats a degree of inanition such as is usual in untreated adrenalectomized animals

may of itself result in low absorption rates and adrenalectomized rats in which appetite and food intake have been well maintained by adequate salt treatment may exhibit normal rates of absorption Hence it may be concluded that this deficiency is secondary to the diminished food intake and that it is not necessarily related directly to adrenocortical function Indirect effects of adrenal deficiency include besides anorexia and digestive disturbances loss of weight and of body fat failure of young animals to grow hemoconcentration diminished renal plasma flow, defective glomerular filtration rates, and rise in blood N P N

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tion of fed carbohydrate was somewhat increased, the glucose tolerance curve continued to be highly abnormal Hence it was considered that a reduction in the rate of gluconeogenesis was chiefly responsible for the effect With the observations of Ingle on force fed adrenalectomized diabetic rats, in which the nitrogen excretion remained fairly high [104] and with repeated indications that large amounts of adrenocortical hormone may interfere with carbohydrate utilization [105] opinion has swung to the view that the effect of adrenal deficiency upon diabetes is caused in part at least by the resumption of carbohydrate oxidation To what extent this is true remains to be demonstrated If lipogenesis is in fact enhanced when the adrenal hormone is absent some resumption of utilization of carbohydrate by this route would be expected Whatever the processes involved or whether the adrenal hormone may be considered truly a diabetogenic agent, the presence of the adrenal secretion appears to be required for the full expression of the diabetic state

Lipid Metabolism Whether the adrenocortical hormone plays any direct role in lipid metabolism is questionable [106] It is true that processes which ordinarily *produce fatty livers in normal animals fail to do so in* adrenal ectomized animals and that the usual responses to ketogenic agents generally are somewhat reduced However cortical extracts or known steroids do not themselves increase liver fat or ketone body production As will be described later in this chapter the adrenal secretion may not intervene directly in these processes but instead it may be required for the rapid mobilization of fat and the formation of ketones under the influence of other factors

Recently it has been reported[107] that although adrenalectomized rats when well fed were able to maintain normal fat stores they lost body fat at a faster rate than control animals when they were severely restricted in food intake Here treatment with cortisone prevented the excessive loss of fat Since untreated operated animals had no difficulty in replenishing their fat depots on resumption of feeding it is evident that the absence of adrenal secretion did not interfere with the ability to store or to draw upon fats in the ordinary way It is possible that the greater utilization of fat could have been a consequence of diminished withdrawal of protein in these circumstances but in the absence of parallel data on nitrogen loss this is not certain

Protein Metabolism Low rates of nitrogen excretion have been observed frequently in adrenalectomized animals in a variety of circumstances Though usually no abnormality is discernible in animals ingesting normal quantities of food diminished rates of excretion have been commonly but not universally [105,108] noted in simple fasting states In phlorhizinized fasting adrenalectomized rats on the other hand the defect is extremely pronounced and it is usually large also in fasting adrenalectomized diabetic animals The eviscerated adrenalectomized rat has been reported to liberate amino nitrogen into the blood at a slower rate [109] Further the negative nitrogen balance which occurs regularly after fractures or other trauma

is not seen in the absence of the adrenals [110,111] nor is the prompt increase in urea formation which occurs after other stresses seen in the adrenalectomized nephrectomized animal [11] These observations indicate no absolute interference with protein catabolism in the absence of the adrenal hormone, but suggest that in conditions in which this process is regularly accelerated, the ability to increase the rate of protein breakdown is impaired [11-114]

Whether the defect in protein metabolism in adrenal deficiency is in the balance between breakdown and synthesis of tissue protein or in the catabolism of the amino acids has been debated The evidence cited above suggests that the major difficulty is in the withdrawal of body proteins, and this has been substantiated by observations of normal rates of urea formation from administered protein or mixed amino acids in a variety of conditions On the other hand, some difficulty in the handling of amino acids particularly by isolated tissues has also been reported It is possible that the maximum performance of the liver and kidney could be affected indirectly by the mild but chronic alterations in blood flow to which even the salt maintained adrenalectomized animal is subject

Functional Alterations

In addition to the biochemical changes just described the adrenal deficient subject gives evidence of a variety of defects which cannot yet be described in metabolic terms [75-77] These include functional alterations in muscle and in the vascular system abnormal physiologic responses of lymphoid tissue and susceptibility to the deleterious effects of stressful or noxious agents of many types

Asthenia and Fatigue of Muscle Weakness and fatigability are characteristic signs of adrenal deficiency in addisonian patients and they have been observed commonly in adrenalectomized animals as well However no complete studies have been made of muscle function as it may be affected by the composition of the blood the blood pressure or other indirect changes in adrenal insufficiency so that it is impossible at present to describe the disability in specific terms In recent experiments the hemodynamic situation has appeared to be of critical importance [115]

Two methods of measuring the degree of muscle failure in adrenalectomized animals have been employed extensively in the assessment of the value of replacement therapy Everse and de Fremery[116] recorded the contractions of the leg muscles of rats to an initial tetanic stimulation followed shortly by several briefer stimuli In these circumstances the muscles of the deficient animals responded normally to the first tetanic stimulation but contracted less extensively in response to the succeeding shocks The failure of the muscle in this acute test may be related to the hemodynamic state for it is prevented by the treatment of the animals for several days with steroids which have a high degree of activity in respect to salt retention and restoration of the blood volume [117] However no reports of the influence of nonspecific factors on this response are available

The second method, that of Ingle,[118,119] differs considerably from the previous one. Here the weighted muscle is subjected to supramaximal *faradic stimulation at regular intervals and the total work done by the* muscle is recorded. In these conditions the normal animal may continue to work for many days but the adrenalectomized animal loses its ability to work in this fashion in a matter of hours. It is doubtful whether the deficiency made evident here is a true fatigue of muscle, for the contralateral unstimulated muscle shares almost equally in the disturbance.[118] The *failure to work is associated with hypoglycemia and depletion of car*bohydrate stores, *and its onset may be delayed by the administration of* glucose.[120] However, these animals also ultimately exhibit circulatory collapse, and the continuous infusion of glucose alone has not been found to improve the total work performance very much.[121] Ingle has expressed the view that although the depletion of carbohydrate stores may be one important factor, failure of other physiologic systems also must play a part. Since changes *in the concentrations of sodium and potassium in the body* fluids do not appear to be critical in the appearance of this failure, the additional processes remain elusive. It is possible that they are related to deficiencies in adjustment of the cardiovascular system to the work loads imposed.

Cardiovascular System. The cardiovascular system of adrenalectomized *animals appears to be less responsive than the normal to most pressor* agents.[1, 123] To what degree functional deficiencies of the heart muscle, arterioles, or capillaries share in producing this disability is not decided, but all may do so. Various changes in cardiac function have been described,[77,124,125] and heart failure has seemed to be the cause of death in *some instances of adrenal insufficiency. Part of these effects may be related* to the increase in potassium concentration of the plasma, but not all are believed explicable on this basis. To judge from available evidence, however, the heart may be abnormally sensitive to changes in ionic composition of the circulation. It has been suggested also that in this condition the heart is unable to increase its work output under circumstances in which *it normally does so.*[126]

Increased permeability of the vascular bed in adrenal insufficiency has been reported frequently. As Chambers and Zweifach[127] have pointed out, this effect may not be caused by changes in the integrity of the capillary walls but by diminution of vascular tone in the arterioles and of vaso*motion in the capillary* bed. The latter effects, reported to occur in adrenalectomized rats before insufficiency is well advanced, and in salt-maintained animals,[128,129] would be such as to impede the venous return and to promote the passage of water and other substances out of the vascular bed. Furthermore, the responsiveness *of the mesenteric arterioles and precapillaries to* epinephrine and norepinephrine, and to a vasoexcitor material from the kidney, have appeared to be diminished or to be lost very quickly. With continued application of norepinephrine or of stressful stimuli the capillaries became quite atonic and refractory, with increasing circulatory stasis.

Fritz and Levine[1,9] suggest that not only are the blood vessels of the adrenalectomized animals unable to maintain a normal response to sympathetic humoral stimulation, but that in failing to do so the vessels become sensitized to the noxious effects of such agents. This deficiency would have the effect of preventing the normal shunting of blood from one area to another as demanded in response to many types of stress. Such defects in the reactivity of the cardiovascular system may well contribute to the tendency to hypotension and to the great susceptibility to shock inducing procedures which are demonstrated by adrenal-deficient subjects.

Lymphoid and Related Tissue The lymph nodes and thymus of the adrenalectomized animal have been reported to be larger than normal when observed some time after operation and the lymphocyte count of the blood also tends to rise[130,131]. More importantly there is universal agreement on the point that the lymphoid tissue does not undergo involution in situations in which this is usual such as in fasting or other stress states nor is the normal fall in blood lymphocytes seen in these conditions[131-133]. In view of the depletion of the lymphoid tissue and the lymphopenia which are induced by adrenocortical steroids or corticotropin or by agents which stimulate the secretion of these hormones the suggestion is strong that the normal values in these respects are a function of continuing adrenocortical activity and that the apparent hypertrophy of lymphoid tissue is the result of removal of this influence. The finding that the lymphocyte count increases more rapidly in adrenalectomized mice under stress than in "nonstressed" adrenalectomized animals suggests that the absence of adrenal excretion may reveal lymphopoietic forces otherwise not detectable[133].

The cortical secretion appears to have widespread effects upon the reactions of tissues of mesenchymal origin and it may also affect endothelial cells. It would be anticipated that adrenal deficient subjects would display alterations of this type in an opposite sense but few of these have so far been described in convincing detail. From observations of the reactions of several types of tissue in anaphylaxis Dougherty[134] considered that the initial inflammatory responses of adrenalectomized animals resembled the normal qualitatively but were much more marked in extent and severity. Clearly the primary reactions of the tissues to insult are not suppressed by adrenal deficiency. However it would appear that some elements of the sequence which tend to limit the extent of the reactions either do not appear or are unable to exert their usual effects.

Resistance to Stress The adrenal deficient subject is remarkably sensitive to the deleterious effects of a wide variety of agents such as trauma cold toxins anaphylactic reactions thyroxin histamine and many drugs. This susceptibility is not directly dependent to any great degree upon abnormalities in the salt or carbohydrate levels in the body since nonspecific supportive measures afford little protection in most situations and since cortical preparations may at times be effective in the absence of material alterations in these factors. Stressful agents such as those mentioned have been shown to promote the activity of the adrenal

cortex in normal subjects Hence it is supposed that the adrenal deficient subject is sensitized by the absence of some protective mechanisms which either are activated by the cortical secretion or more likely, are able to be fully effective only in the presence of sufficient amounts of the hormone Undoubtedly these mechanisms concern the homeostatic responses of the tissues to changes in local environment, perhaps for resistance to many types of stress it is the reactions of the mesenchymal and vascular systems which are most important, but the essential nature of the processes affected is quite unknown

Effects of Cortical Extracts and Adrenal Steroids

Because of the variety of effects which may be induced by adreno cortical extracts and in view of the number of active steroids known com plete understanding of the physiologic effects of these materials requires comparative assays of the several compounds over the whole range of activities This task has not yet been completed but a summary of available evidence is presented in Table 4 The nature of the effects measured will be discussed in the following sections

Life Maintenance and Kidney Function

Maintenance of Life The six adrenal steroids described in Table 4 and progesterone as well are able to maintain life and a semblance of health in adrenalectomized animals Insofar as the relative effectiveness of the steroids in this respect has been measured quantitatively, DOC and perhaps the amorphous fraction have appeared to be the most potent The prin cipal mechanisms affected by the several steroids may differ however As noted below, DOC seems to have its primary action on the retention of salt and by virtue of this activity to preserve the blood volume kidney func tion and appetite An animal maintained with DOC develops hypoglycemia readily and remains abnormally sensitive to all forms of stress differing but little in these and kindred respects from animals maintained only by adjustment of salt intake On the other hand adrenalectomized dogs given cortical extract or fairly large amounts of cortisone but little or no salt, may be revived from crisis or kept in apparent good health for many weeks without there necessarily occurring any correction of the abnormal concentrations of sodium chloride and potassium in the plasma [136 139] The physiologic actions of the hormone which are effective in the support of adrenalectomized animals under these conditions have not been clarified

The importance of the retention of salt in the maintenance of life may be indicated by the general parallelism in the effectiveness of the adrenal steroids in these two respects (Table 4) Cortisone alone except perhaps in very large dosage has not always appeared to constitute adequate re placement therapy in adrenalectomized dogs or in patients with Addison s disease but a combination of small amounts of DOC with cortisone has been reported to be quite effective In young adrenalectomized rats on the other

Table 4

RELATIVE POTENCIES OF THE ADRENAL STEROIDS

	Compound F Hyd cort o	*Compound F* C t	*Compound B* C t o te o e	*Compound 1* 11 Dehydro- o t t	*DOC* 11 Des- o y t costerone	*Compound S* 11 Des- oxy t	*Amorphous Fraction*
Maintenance of adrenalectomized dogs	+	3	15	12	100		+++
Growth in adrenalectomized rats	219	100	108	+	++		++
Salt Metabolism Excretion ratio of radiosodium to radiopotassium Sodium balance	 7 +	 6 ±	 14 ++	 7 ++	 100 ++++	 8 ±	
Glycogen deposition	155	100	54	47	0-2	0	0
Diabetogenic activity	+++	+++	++	++	±		
Muscle work performance (Ingle method)	160	100	46	32	2	2	10
Muscle fatigue prevention (Everse-de Fremery method)	4		6		100	+	25
Depletion of lymphoid tissue	+++	+++	+++		0		
Protective action against cold		100	9	33	8		+
water load		+++			+		+
anaphylaxis	+++	+++			0		
egg white reaction (intact rats)	133	100		40	0		

These observations have been drawn principally from the papers of Dorfman Kuizenga [5] and others [1 7 1 8–133] with some additional evidence from other investigators

hand good growth may be obtained with any of the six adrenal steroids and no extreme differences in potency among the compounds is apparent The effectiveness of the adrenal steroids in respect to effects upon survival and health has been most difficult to evaluate quantitatively and in particular the activities of other 11 oxysteroids than cortisone have not been fully explored Hence at present it is not at all certain whether one of the

steroids might in reasonable amounts act as a "complete" hormone, or whether the combined actions of two factors would more closely simulate the natural secretion of the adrenal cortex

Electrolyte Metabolism Restoration of the salt balance in adrenal deficient subjects by cortical extracts and extra retention of salt in subjects with intact adrenals given either cortical extracts or corticotropin have been observed many times In both normal and adrenalectomized animals DOC duplicates this effect and remarkably small doses of this steroid may be shown to diminish the excretion of sodium [140] This effect appears to be the result of an increase in the rate of resorption of sodium by the tubules [141] The action of adrenal steroids on the exchange of salt is not confined to the kidney however for corticotropin or DOC will diminish the concentrations of sodium and chloride in the sweat [138 142] and in the saliva [143] and desoxycorticosterone acetate (DCA) has been reported to diminish fecal sodium [144]

To what extent the other active adrenal steroids share in this type of activity has been a moot question In intact subjects large doses of cortisone or hydrocortisone have several times been observed to cause a temporary increase in sodium excretion rather than retention of salt [140 145 146] and this has led to a common belief that the 17 hydroxysteroids are inactive in the usual sense in this respect However Conn, Louis and Fajans[147] have reported that hydrocortisone induced a considerable degree of salt retention in a normal subject and several observers agree that cortisone also is active in adrenalectomized animals [138 141 148] In the latter instances the effectiveness of cortisone was one-twentieth to one thirtieth that of DOC

The reason for the occasional reversal of the sodium effect with the 17 hydroxysteroids is not clear The dosage range tested may be important for in conditions in which larger doses of the oxysteroids appeared ineffective smaller amounts tended to induce retention of sodium [149] The degree of activity of DCA on the retention of radiosodium was diminished as the amounts of salt given were increased [150] so it is possible that high sodium loads would tend to obscure the weaker effects of the other steroids Still another factor may be the fluid load Cortisone and other adrenal steroids can act as diuretic agents especially in conditions of overhydration and in some instances in which the amount of sodium excreted was somewhat increased the concentration of sodium in the urine was in fact much diminished Here a tendency to increase the resorption of sodium may have been obscured by the large urine flow In the absence of information on the exact roles of the steroids in the excretion of water as well as of salt and of the influence of the amounts of salt and water in the body on these effects it is obvious that any conclusions as to the existence and nature of an antagonism between cortisone and DOC in these respects may be premature

The sodium retaining properties of adrenal steroids other than cortisone and DOC are even less well known In two sets of parallel observations corticosterone was reported to cause sodium retention in conditions in which hydrocortisone induced loss of sodium [145 146] and corticosterone has been

held to be a more effective agent than cortisone in the maintenance of deficient animals Hence it is possible that the two 11 oxysteroids which lack the 17 hydroxy group would be more active with respect to sodium metabolism than the cortisone type 11 Desoxycortisone which is found in the adrenal gland but has not been shown to be secreted by it has been considered to resemble DOC in its properties but if so its activity evidently is much less than that of the latter compound [151] The amorphous fraction also has been said to be very active in maintaining life so there is still the possibility that unidentified substances from the adrenal may contribute to the activity of cortical extracts Obviously it is not yet entirely clear whether the sodium retaining effects of the adrenal cortex either with or without corticotropin can be accounted for by the activity of the steroids known to be secreted by the gland

The role of the adrenal steroids in the metabolism of potassium appears to be complex and is but little understood All of the steroids and corticotropin as well, have been reported frequently to increase the excretion of potassium both in intact and in adrenal-deficient subjects No very marked differences in the potencies of the several adrenal steroids have been noted in this respect Part of this effect may be ascribed to an increase in the concentrating capacity of the kidney for this ion [83] However under some conditions the amounts of potassium excreted may not be increased and yet diminution of the plasma potassium level is observed [141 152] Hence it has been proposed that the hormone may act in an extrarenal capacity, presumably promoting the movement of potassium into the cells in some or all tissues With intensive treatment with the oxysteroids on the other hand large amounts of potassium may be lost from the body The depletion of intracellular potassium here may perhaps be correlated with liberation of protein from the tissues

Whatever the mechanisms involved, it should be noted that depletion of the plasma potassium to dangerous levels may be seen during the administration of large amounts of corticotropin or adrenal steroids Fortunately the symptoms of this deficiency may usually be corrected by judicious treatment with potassium salts

Water Balance The several adrenal steroids may in different circumstances either increase or diminish the excretion of water Where sodium is being retained in any quantity water tends also to be retained and at times a distinct excess of extracellular fluid may be produced On the other hand if hydration is complete or particularly if physiologic saline has been given the cortical factors tend to induce diuresis Additionally when large amounts of steroid especially DOC are used chronically a state resembling diabetes insipidus may be seen here the large urine volume appears to be principally the result of polydipsia following the retention of salt Gaunt Birnie and Eversole[90] and their associates[94] have summarized the indications that cortical steroids are active diuretic agents presumably diminishing the tubular resorption of water and that the oxysteroids rather than DOC are the more effective substances in this respect

Possible Extrarenal Effects upon Salt and Water Metabolism While the effects of the adrenal steroids upon the concentrations of electrolytes and water in the fluids and tissues of the body have appeared in most instances to be explicable on the basis of changes induced in kidney function and the resulting shifts in osmotic balances,[85, 153] a number of investigators have considered that there must also be extrarenal effects especially with respect to movements of water and potassium Swingle and his associates[136, 139] have pointed out that extensive alterations in plasma or extra cellular fluid volumes can occur in hormone treated adrenalectomized animals without concomitant restoration of the electrolyte levels Alterations observed in the proportions of extra and intra cellular water in adrenalectomized animals with and without treatment were considered by Gaudino and Levitt[86] to be too large to be explained by changes in plasma electrolytes Recently, Bloodworth[154] has reported that the extracellular fluid space appeared to be increased at the expense of the intracellular compartment when adrenocortical extract (but not DCA) was given in experiments to normal dogs The increases were of such magnitude (20 to 40 per cent) as not to be explained adequately by the renal retention of sodium which could take place in the short time of the experiment The frequent failure of changes in serum potassium to be correlated with the excretion of potassium has already been mentioned Further, Ingle Nelson, and Kendall[155] have reported that cortical extracts will diminish the extent of the increase in serum potassium which occurs in adrenalectomized nephrectomized rats These observations taken together tend to suggest that the distribution of water and perhaps of potassium may be influenced by cortical hormone in some more direct fashion as well as indirectly through alterations in electrolyte balance

Effects of the steroids upon the excretion of sodium and chloride by other routes than the urine were discussed under Electrolyte Metabolism Evidence that movement of sodium within the body may be affected directly is not strong although Flanagan Davis and Overman[156] considered that the changes in extracellular electrolytes seen in dogs going into and recovering from insufficiency were too large to be caused only by alterations in the amounts excreted in the urine Changes in the permeability of certain tissues to sodium have also been postulated [157, 158]

The implications of these and related observations have been discussed by several investigators [76, 86, 90, 141] If the adrenal steroids do have widespread effects throughout the body upon movements of water and electrolytes the mechanisms remain obscure Possibly these actions could be related in part to the maintenance of capillary tone and reactivity or changes might be induced in the concentrations of nondiffusible substances within the cells or the hormones might affect the metabolic systems which maintain the differential permeability of the cell membranes

Carbohydrate and Lipid Metabolism

Maintenance of the carbohydrate levels in the blood and tissues of adrenalectomized animals and increases in the carbohydrate content of the

tissues of normal animals treated with cortical extract were first reported by Britton and Silvette in 1932 [159, 160] In this early work however it was difficult to distinguish between the effects of the hormone upon appetite or the general condition of the animals and those upon carbohydrate metabolism per se The nature of the activity of the adrenal steroids in this respect was first clearly outlined by Long Katzin and Fry in 1940 [96]

Gluconeogenesis In fasting animals, either normal or adrenalectomized and maintained with salt, the administration of moderate amounts of cortical extract or of the 11 oxysteroids is followed by some elevation of the blood glucose and by the accumulation of considerable amounts of glycogen in the liver (Table 5) Since the muscle glycogen is not diminished in these

Table 5

EFFECTS OF CORTICAL EXTRACT UPON CARBOHYDRATE STORES AND NITROGEN EXCRETION IN NORMAL FASTING RATS

	Blood Glucose	*Liver Glycogen*	*Muscle Glycogen*	*Total Carbohydrate**	*Nitrogen Excreted (12 hours)*
	Mg per 100	Mg per 100 Gm body wt	Mg per 100 Gm body wt	Mg per 100 Gm body wt	Mg per 100 Gm body wt
Untreated	74	7	253	301	54
Cortical extract †	*108*	*79*	*260*	*390*	*81*
Increase	34	72		89‡	27‡

* Calculated on the assumption that blood glucose and muscle glycogen each are distributed in 50 per cent of the body weight with no significant increase in tissue glycogen

† Given hourly during last 12 hours of a 24-hour fasting period

‡ G N (extra carbohydrate extra nitrogen) = 3 3

This table is based upon data contained in the article of Long Katzin and Fry [96]

conditions the glycogen laid down in the liver must be newly formed from noncarbohydrate precursors In rats and mice in standardized conditions the increase in liver glycogen is closely related to the dose of hormone so that this effect of the adrenal steroids now forms the basis of several widely employed methods of assay for adrenocortical activity [65] The substances which are active here are sometimes referred to as glucocorticoids As shown in Table 4 this property is virtually confined to those steroids having an oxygen atom at C 11 Those also bearing a C 17 hydroxy group are more potent than the others, and most investigators agree also that hydrocortisone is the most active steroid in the group

A similar effect of adrenal steroids upon gluconeogenesis has been demonstrated in fasting phlorhizinized adrenalectomized animals [161–163] Here the low rates of excretion of both glucose and nitrogen may be restored to normal by treatment with any of the 11 oxysteroids In these conditions DOC also has some degree of activity and it is possible that some part of the effects seen in these animals is the result of improvement in the hemo-

dynamic state and the consequent increase in kidney and liver function No noteworthy effects of the steroids in intact phlorhizinized animals have been reported

In adrenalectomized mice given insulin the incidence of convulsions may be greatly reduced by administration of cortical extract or of some 11 oxysteroids [164] This contra insulin effect has been correlated with the accumulation of glycogen in the liver [16] and it may be supposed that it is caused largely by the provision of extra glucose via gluconeogenesis

The mechanism by which the corticosteroids induce gluconeogenesis has not been precisely defined When the nitrogen excretion has been measured concurrently with the deposition of glycogen in the liver or the excretion of glucose in phlorhizinized animals the loss of nitrogen has been found to be increased proportionately, and all of the new carbohydrate could have come from the extra protein indicated to have been metabolized (Table 3) Thus the most probable source of the carbohydrate produced in fasting animals under the influence of the steroids is the proteins of the body In phlorhizinized adrenalectomized animals given alanine or lactate, the amounts of glucose excreted were reported to be increased by treatment with cortical extracts but since the excretion of exogenous glucose was affected similarly this effect was interpreted as being caused by diminution in the oxidation of carbohydrate and its intermediates rather than by increased gluconeogenesis [16] No convincing evidence has yet been offered to indicate that the administration of steroids to normal animals enhances the conversion of exogenous proteins or amino acids to carbohydrate In view of these facts it seems likely that the principal effect of the steroids is upon the breakdown of body protein rather than upon the process of gluconeogenesis itself and that new formation of carbohydrate follows upon the provision of available substrate

Diabetogenic Effects The gluconeogenetic activity of the adrenal steroids described above is best observed in fasting animals When the subjects are fed it is possible that additional effects of the hormones come into play In acute experiments in which carbohydrate is fed very large amounts of glycogen are deposited in the liver and muscle glycogen too may be somewhat increased The R Q usually is low in such animals suggesting an interference with the utilization of carbohydrate [96] With prolonged treatment with large amounts of hormone diminution in the glucose tolerance and glycosuria may be produced These diabetogenic effects of cortical extracts were first demonstrated in the resumption of glycosuria in adrenalectomized depancreatized animals and in the exacerbation of the diabetes in partially depancreatized rats [98] Later, with quite large amounts of steroid or of corticotropin Ingle[105 166] and his associates[167] found that force fed intact rats could also be made glycosuric The 11 oxysteroids are by far the most effective diabetogenic agents but DOC is not entirely without activity [163]

The diabetes induced by adrenal steroids appears to differ somewhat from pancreatic diabetes in that the animals are enormously resistant to

insulin and such associated effects as diminution in glucose tolerance ketosis and loss of water, salts and nitrogen are often not commensurate with the degree of glycosuria Since in balance experiments the increase in nitrogen excretion with adrenal steroids has usually been too small to account for the amounts of glucose excreted it has been supposed that the hormone must interfere with the utilization of carbohydrate Recently however Welt et al [169] giving radioglucose to cortisone-treated rats found that the principal effect of the hormone was to increase greatly the dilution of the administered carbohydrate by nonisotopic glucose hence the rate of gluconeogenesis from unknown precursors must have been increased commensurately Little change was seen in the oxidation of the radioglucose The question is still open whether in addition to increasing gluconeogenesis the hormone may interfere with the utilization of glucose via fat formation

While the diabetogenic effects of the adrenal steroids or corticotropin may be readily demonstrated in rats in other species the effects have been less marked On the other hand anterior pituitary extracts or purified growth hormone containing little or no corticotropin are strongly diabetogenic in intact cats and dogs as well as in partially depancreatized rats but not in intact rats The "pituitary diabetes is not seen in adrenalectomized animals but it has been reported in animals maintained with minimal amounts of cortical extract [96] Recently Engel et al [170] found that growth hormone may be rendered diabetogenic in the intact force-fed rat if some corticotropin is given as well and that the degree of glycosuria so induced is related to the amount of growth hormone rather than to the amount of corticotropin A similar permissive role of the adrenal hormone has been reported with respect to the R Q depressing and glycogen conserving effects of pituitary extract or growth hormone[171 172] and with respect to diabetogenic effects of certain estrogens [173] These observations raise a serious question as to whether the adrenal steroids act as primary diabetogenic agents or whether instead they are necessary in some indeterminate amounts for other factors to take effect As will be seen shortly a similar situation seems to hold for the action of adrenal steroids on nitrogen catabolism Whether the mechanisms activated by the adrenocortical hormone are the same in all instances is not known

Lipid Metabolism Little is known of the possible effects of the adrenocortical hormone upon lipid metabolism [106] *If the hormone tended to diminish* the utilization of carbohydrate it would be expected that the utilization of fat would be increased but few signs of such activity are evident Neither the known adrenal steroids nor cortical extracts of the usual type produce ketosis except perhaps during severe steroid diabetes nor have they usually been observed to increase the mobilization of fat to the liver Corticotropin on the other hand has been reported in some instances to induce ketonemia and in prolonged experiments an increase in liver or body fat It may be that the adrenal secretes an unidentified ' fat factor as maintained by Hartman and Brownell [2] but this view has

not received general acceptance Cortical hormones do however appear to be required for the demonstration of adipokinetic activity of other factors [174] From present evidence it seems possible that the reported activity of some corticotropin preparations could result from the action of another pituitary factor working with the adrenal steroids and that the occasional observations of adrenal steroid activity in these respects are expressions also of some sort of indirect or synergistic role

The obesity frequently seen in Cushing's syndrome has not been reproduced in animals given adrenal steroids Since in both man and animals an increase in appetite often accompanies the administration of cortisone, it seems likely that the generalized obesity could be due to an imbalance between food intake and activity The peculiar localized deposition of fatty tissue which may be seen in this condition is not understood

Protein Metabolism

When any of the 11 oxysteroids or corticotropin is given in moderately large amounts to man or to animals a considerable increase in nitrogen excretion usually follows within a few hours This occurs mainly in the form of urea or in birds as uric acid In man there is also an increase in uric acid excretion but the factors affecting the action of cortical hormones on purine metabolism have not been studied in any detail

The increase in general catabolism of protein under the influence of adrenocortical hormone is seen in both fed and fasted animals, with continued treatment serious losses of body tissue may be induced This catabolic effect is not however obligatory It tends to diminish with time so that after some days or weeks a negative nitrogen balance may or may not be evident [105] it is less apparent when the diet is high in protein [175] it may be abolished by increasing the food intake or in acute experiments by administering glucose or amino acid mixtures [176] and it has been reported to be prevented by increasing the potassium intake [177] Evidently the extent of the increase in protein catabolism induced by adrenocortical hormone is strongly conditioned by the metabolic state of the subject

The converse of this relationship is also true for the catabolic effects of other agents upon nitrogen metabolism appear to be determined to a considerable extent by the amount of adrenal hormone available The permissive role of the adrenal in the post traumatic loss of nitrogen has been referred to earlier In extensive studies of this phenomenon in intact as well as in adrenalectomized rats Engel[11, 178] has shown that not only is cortical hormone required for the catabolic reaction but that with mild degrees of stress (such as moderate hypoglycemia or the injection of small amounts of formalin) cortical extract or corticotropin hastens and augments the catabolic response This investigator suggests that fasting itself might be regarded as a stress which could give rise to the characteristic metabolic pattern of injury only in the presence of cortical hormone In the experiments of Engel and of others also the magnitude of the effect has appeared to be dependent more upon the degree of stress than upon the amount of

hormone provided that some minimum quantity was present However, this minimum amount appears to vary inversely with the severity of the stress and it is possible that with mild departures from the basal' state the amount of hormone would be found to be a determining factor also Thus whether a catabolic effect of cortical hormone will be seen depends not only upon the intensity and duration of treatment and upon the nutritional state of the subject but also very much upon the degree of stress if any to which it has been subjected

The mechanisms by which either cortical hormone or the various stresses induce loss of nitrogen are largely unknown Most of the tissues of the body appear to be affected by the hormone in some degree [179–181] The lymphoid tissue undergoes the most profound depletion in all conditions Although during fasting the liver loses a greater proportion of its nitrogen than do most tissues excess of cortical hormone does not accentuate this depletion, but rather tends to prevent it (Table 6) Also cortical hormone hastens

Table 6

EFFECT OF ADRENALECTOMY AND OF CORTICAL EXTRACT UPON THE LOSS OF NITROGEN FROM THE TISSUE OF FASTING MICE

Group	*Alterations in Nitrogen Content during 48 Hours of Fasting*					
	Liver		*Carcass*		*Lymphoid Tissue*	
	Mg per 100 Gm Lost	Final (Per Cent of Initial N)†	Mg per 100 Gm Lost	Final (Per Cent of Initial N)†	Mg per 100 Gm Lost	Final (Per Cent of Initial N)†
Intact	−39	78	−340	88	−9 4	69
Adrenalectomized	−31	83	−120	96	+6 4	118
Adrenalectomized given cortical extract	−23	87	−230	92	−13 7	55
Average standard error	±6	±4	±50	±2	±1 0	±5

10 to 12 animals per group
† Intact unfasted controls
This table is based upon data contained in the article of White and Dougherty [179]

the regeneration of liver tissue in partially hepatectomized animals Hence it may be inferred that the hormone favors the movement of protein from the rest of the body toward the liver The cortical factors and the pituitary growth hormone are mutually antagonistic with respect to skeletal growth as well as to nitrogen balance and in young animals an excess of cortical hormone induces dwarfism with a relative splanchnomegaly Thus the peripheral tissues seem in general to be rather more sensitive to excess cortical hormone than are the viscera

There has been little evidence so far to suggest any effect of the hormone upon the catabolism of amino acids themselves or upon the metabolism of exogenous protein and most investigators have considered that the hormone must either increase the breakdown of protein or suppress its synthesis in most or all tissues When isotopic glycine has been given to animals or human subjects treated with cortisone or corticotropin or to patients with Cushing's syndrome a considerably larger proportion of the isotopic nitrogen has been excreted than in the control subjects[182–184] This has been interpreted to mean that a smaller proportion of the amino acids in the body was being synthesized into protein However in fasting animals this effect was accompanied by a large dilution of the excreted isotopic nitrogen with nonisotopic nitrogen from the body[18] indicating that in these conditions the principal effect was upon protein breakdown It is possible that both in fasted and fed subjects the increased excretion of labeled nitrogen could have been due to a washing out of nitrogen through the delivery of excessive quantities of amino acids (or protein) to the liver This interpretation is consistent with the finding reported by Clark[184] of increased quantities of isotope in the liver protein and nonprotein nitrogen and diminished amounts of isotope in the nitrogen of the carcass tissues of cortisone treated rats It is supported also by the observations of Roberts[185] that the tissues of adrenal hormone–treated animals liberated more protein into the medium during incubation *in vitro* and that in partially hepatectomized rats the regeneration of liver protein was hastened and the fall in serum albumin prevented by treatment with adrenal steroids

The conclusion to be drawn from this diversity of observations seems to be that the cortical hormone does not itself directly stimulate the catabolism of amino acids or protein but that it serves to labilize or sensitize the body proteins so that they are more readily drawn upon when other agents largely unknown tend to enhance the movement of protein Whether the process affected is catabolic or antianabolic in nature is still debatable In view of the intimate relationship between the actions of adrenal steroids and of stress in protein metabolism and the nearly absolute lack of knowledge concerning the mechanisms by which the various stresses exert their effects further generalizations concerning the exact site of action of these hormones are scarcely warranted at the present time

Functional and Morphologic Effects

As indicated earlier cortical hormones display a wide range of activities which are as yet but little understood One of the major problems of adrenal physiology is that of defining the relationship of these effects to the biochemical and metabolic activities which have been described above

Muscle Function In two types of muscle function tests which have been examined in some detail cortical hormones are able to improve the performance of adrenalectomized animals, but in neither case has any effect been demonstrated upon muscle function in normal animals In the Ingle test[119 186] the ability of adrenalectomized nephrectomized rats to sustain

continued muscular activity is measured Here a wide range of responses has afforded the opportunity of measuring the relative potencies of the steroids in a quantitative manner As indicated in Table 4, the relative activities in this test parallel remarkably closely those found in respect to glycogenesis However the administration of glucose does not reproduce the effects of the steroid and moreover the most active steroids generally achieve a maximal effect short of complete restitution Evidently, under these conditions other factors than the rate of gluconeogenesis must limit the ability of the muscle to continue working The conditions of this test are such as to constitute a serious generalized stress to the organism so it is likely that some fundamental activity of the hormone is common to the effects upon glycogenesis and to the ability of the animal to continue working and probably also to the promotion of some aspects of general resistance to stress

In the Everse–de Fremery test[116] where the immediate neuromuscular response to brief stimulation is observed the reported order of the effectiveness of the several steroids has been the reverse of that seen in the Ingle test The steroids here were given over a four day period to otherwise untreated deficient animals The fact that the relative activities of the steroids have appeared to be similar to those seen in respect to salt retention suggests that this effect could be related to the maintenance of normal salt concentrations in the body fluids or extracellular fluid volume and blood pressure

This divergence in relative activities of the cortical steroids in two different tests of muscle function indicates that the cortical factors act on this system in more than one way This conclusion is in accord with recent observations made in adrenalectomized dogs by Goldstein Ramey and Levine [115] In this work it was observed that the responses of the gastrocnemius muscle to stimulation could be maintained or restored when the blood pressure was held at moderate levels and that this could be achieved by any of several means However adrenalectomized animals supported only by DOC could maintain neither the blood pressure nor normal muscle contractions when stimulation was continued for any length of time Thus the initial responses of the muscles of hormone-treated adrenalectomized animals may well be a function of the maintenance of the blood pressure through protection of the animals against loss of salt However for continued activity there must be additional support of the circulation achieved by other means This could be in part at least through adjustment of the cardiovascular system to the demands of continued muscle work

Functional and morphologic effects have also been demonstrated on the cardiovascular system [76 1 3 1 7 1 9] The effects upon lymphatic tissue long studied in the laboratory [13 187–19] and other effects upon the hemopoietic system are described elsewhere in this volume The capacity of cortisone or corticotropin to alter the usual course of inflammation [134 19–196] and of other stresses depends upon a mechanism which has not yet been elucidated Because most of the following chapters deal with various aspects

of this major adrenocortical function it is not included here Certainly one of the significant results of the development of cortisone is the stimulus to a renewed study of inflammation

Summary

Early studies of the physiology of the adrenal cortex revolved largely around the effects upon electrolyte metabolism which are so important for the maintenance of life A little later, increasing emphasis was given to those aspects of the metabolism of carbohydrate protein and fat in which the adrenal hormone is active here present evidence indicates that to a considerable extent the hormone acts not so much as a prime mover but rather as a necessary adjuvant to other physiologic processes Most recently, the therapeutic success of the hormone in certain conditions of disease has turned attention to effects of the hormone upon some aspects of cellular function which though not completely unforeseen had been largely unsuspected In all of these fields there are still large areas in which our understanding is limited The outstanding problem however is that the effects of the adrenal hormone in these several phases of physiology are still unrelated by any general hypothesis concerning their mechanisms Logically it may be expected that some common ground will be found for all of these manifestations that some one type of reaction is controlled by the hormone The wide variety of effects demonstrated by the hormone may be produced not by a multiplicity of activities but, rather by the nature of the different tissues and systems affected and the circumstances in which the action of the hormone is observed

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2

Pharmacologic Aspects of Adrenocortical Hormones in Man, and Their Effects in Adrenal Insufficiency

George W Thorn, Dalton Jenkins, John C Laidlaw, Frederick C Goetz, Joseph F Dingman, Walter L Arons, David H P Streeten, and Brian H McCracken

The importance of the adrenocortical steroids as essential mediators of metabolic processes is well established In the treatment of adrenocortical insufficiency these hormones are capable of restoring severely ill patients to a state of health that is remarkably near normal In the wider field of inflammatory diseases their action is no less dramatic although the indications for their use and their ultimate place in the therapeutic armamentarium are not yet clearly defined Experience has emphasized the necessity for exercising unusual care in initiating or terminating a therapeutic trial with these agents Regardless of the extent to which they may eventually be employed in the everyday practice of medicine the necessity for understanding as clearly as possible their mode of action in the human body remains This chapter is presented therefore in the hope that a reassessment of the more important pharmacologic aspects of the action of the adrenocortical hormones may prove useful to the practicing physician The structure of the C-21 adrenal steroids has been shown in Figure 1 of the preceding chapter

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Supported in part by grants from the National Institutes of Health United States Public Health Service The Armour Laboratories Ciba Pharmaceutical Products Merck and Co Inc The Upjohn Company and the Eugene Higgins Trust through Harvard University

Printed with changes from Medical Progress reports formerly published in The New England Journal of Medicine Volume 248 Numbers 6–10 14 15 February–April 1953 under the title Pharmacologic Aspects of Adrenocortical Steroids and ACTH in Man

11-Desoxycorticosterone

The first adrenal steroid to be synthesized was 11-desoxycorticosterone [1] In this instance the synthesis of a steroid hormone was accomplished prior to its identification and isolation from adrenal gland extracts The important physiologic processes that this hormone controls are well established Whether or not a hormone of this exact chemical composition is secreted by the normal human adrenal gland has been open to serious question Because of its marked potency one might expect to find only traces of desoxycorticosterone (DOC) in adrenal extracts or perfusates It has been considered that the virtual elimination of sodium from the urine of normal subjects treated with corticotropin probably indicated the secretion of an adrenal steroid more salt retaining than either the 11 or 11 17 oxysteroids However, recent experiments[3] have shown that the intravenous infusion of hydrocortisone (compound F) in a normal subject at the rate of 12 mg per hour is capable of inducing profound sodium retention hence the occurrence of a marked reduction in sodium excretion after intensive stimulation with corticotropin does not necessarily require the secretion of DOC like steroids

On the other hand the probability that the adrenal glands secrete DOC is suggested by the experiments of Hechter et al [4] who have detected this steroid in blood after perfusion of isolated beef adrenal glands Recent experiments of Simpson et al [5] have demonstrated that a new and highly potent electrolyte regulating compound is present in adrenal gland extracts and in the adrenal venous blood of laboratory animals This compound was found to be distinct from cortisone hydrocortisone corticosterone and DOC was much more potent in its salt retaining capacity than any of these agents and appeared to be responsible for most of the electrolyte regulating activity of the original extract Finally it should be remembered that the amorphous fraction remaining after the preparation of adrenocortical aqueous extracts contains highly effective and as yet unidentified electrolyte regulating substances [6] Although under circumstances of maximal adrenocortical stimulation it is possible that electrolyte regulation could be mediated by the quantity of hydrocortisone-like substances secreted in all likelihood under normal circumstances electrolyte regulation is effected through the action of more potent salt retaining substances It must be admitted that whereas the exact status of DOC as a natural mineralocorticoid is still uncertain it remains the most potent steroid available today for the control of sodium and potassium urinary excretion

Physiologic Actions When administered in adequate dosage to normal subjects as well as to patients with adrenocortical insufficiency DOC produces definite changes in electrolyte and water balance as regulated by the kidneys sweat glands salivary glands gastrointestinal tract and in all probability body cells in general As might be anticipated these effects are demonstrated much more readily in patients with Addison s disease than in subjects with intact adrenal glands

Kidney The renal effects of DOC in man consist of the retention of sodium chloride and water and an increased excretion of potassium [7] Although changes in the urinary excretion of calcium and phosphorus may occur, the effects upon total balance are variable and usually of a minor degree In patients with adrenocortical insufficiency DOC produces as a direct result of the restoration of electrolyte and water balance, an expansion of plasma and extracellular fluid volumes a gain in body weight, and a rise in blood pressure [8,9] In addition renal plasma flow glomerular filtration rate, and the clearance of urea and endogenous creatinine are enhanced The studies of Pitts[10] suggest that these changes in renal hemodynamics are secondary to the restoration of total body electrolyte and water content resulting from the primary action of the hormone on the renal tubule Thus, it appears probable that the primary effect of DOC on kidney function is the enhancement of sodium reabsorption and of potassium elimination by the renal tubules Indeed patients with advanced kidney disease characterized by enormous losses of urinary sodium and chloride (salt losing nephritis)[11] are unable to respond to DOC administration with either sodium retention or an increased output of potassium

The *mechanisms by which this steroid influences the regulation of* electrolyte excretion by the renal tubules have been investigated by Pitts [1] These studies carried out in adrenalectomized dogs indicate that adrenocortical steroids are capable of regulating the reabsorption of approximately 2 per cent of the total tubular load of filtered sodium It appears likely on the basis of the response engendered by the stress of moderate acid loading (for example with ammonium chloride) that DOC influences the tubular exchange of sodium potassium and hydrogen ions However the modifying influence exerted by this steroid on the renal actions of mercurial diuretics and Pitressin suggests that the hormonal action on electrolyte excretion is not confined to its effects upon the ion exchange mechanisms A direct effect upon the tubular processes responsible for ammonia secretion may also occur [13] The locus of these actions is considered to be the distal tubules

Studies carried out in normal human subjects show a definite effect *upon the renal excretion of electrolytes within two to four* hours of intramuscular[14] as well as intravenous[3] administration of DOC It is of interest that the administration of desoxycorticosterone acetate (DCA) to human subjects during the *rigid restriction of sodium intake produces little or no* rise in the urinary excretion of potassium and has no effect upon the external exchange and internal distribution of water [15,16] These results suggest the existence of a renal mechanism that controls the excretion of *both sodium* and potassium and is subject to the influence of DOC as suggested by Pitts[1] furthermore it is apparent that the effect of the hormone upon potassium elimination is conditioned by the degree of concurrent sodium retention

In contrast to patients with Addison s disease in whom the effects described are ordinarily obtained at a dosage level of 1 to 3 mg per day normal subjects usually require the administration of considerably larger

[illegible] 19 [illegible] per [illegible] or more [illegible] effect [illegible]. Moreover, the prolonged administration of [illegible] normal [illegible] [illegible] followed [illegible] an escape from this effect [illegible] and [illegible] A [illegible] normal potassium [illegible] ordinarily follows that of sodium. [illegible] the prolonged administration of large amounts of [illegible] may produce a marked increase in [illegible] and [illegible] for the syndrome. [illegible] has been ascribed to excess sodium retention and [illegible] alternative explanations have been presented. A similar [illegible] less marked effect has been described in [illegible] per [illegible] large amounts of [illegible].

Sweat. [illegible] sweat [illegible] the concentration of sodium and chloride [illegible] certain circumstances can be [illegible] with the loss of adrenocortical activity. A marked fall in sodium and

Table [illegible]

Effect of Desoxycorticosterone Acetate upon the Salivary Ratio of Sodium to Potassium

Treatment	Ratio of Sodium to Potassium
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
DCA, [illegible]	[illegible]

chloride concentration and a rise in potassium concentration are produced by [illegible] the normal [illegible] as well as in the patient with Addison's disease. In contrast to the reversed effect upon the renal excretion of electrolytes however, continued administration of the hormone to normal subjects is not accompanied by an "escape" from sodium retention and potassium loss.

Saliva. Changes in the electrolyte composition of the saliva follow the pattern found in sweat, i.e., DCA causes a decrease in sodium and chloride concentration and a rise in potassium concentration. Frawley[illegible] has demonstrated the usefulness of determining the ratio of sodium to potassium in saliva as a measure of activity of the adrenal [illegible] hormones. The effect of DCA [illegible] normal [illegible] shown in Table [illegible].

Gastrointestinal Tract. The adrenal hormones presumably affect the intestinal secretion in a manner comparable with the effect upon the salivary and sweat glands. Since most of the electrolytes secreted into the intestinal tract are reabsorbed, however, there is ordinarily little opportunity to observe this effect. Berger et al.[illegible] raised the sodium [illegible] by administering a cation exchange resin to 3 patients, and then were able to demonstrate a decrease in fecal sodium [illegible] DCA administration. We have carried out a similar study in a patient with Addison's disease and

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in electrolyte balance produced by intensive renal tubular sodium retention and potassium loss

However, it has long been recognized that DOC may exert an effect upon intracellular electrolytes and water independent of its effect upon renal tubules Consistent with this is the fact that Woodbury [5] has succeeded in demonstrating a change in the tissue content of sodium in the nephrectomized rat receiving DCA

Recent studies by Luft [29] in which simultaneous measurements of sodium balance and total Na^{24} space were carried out in patients with intact adrenal glands receiving large doses of DCA over prolonged periods provide further evidence for extrarenal actions of this steroid Although the initial period of marked sodium retention was followed in all cases by an escape to a state of normal balance and even negative balance during continued DCA administration the distribution space of radio odium steadily enlarged The lack of correlation between external balance and internal distribution must signify a direct effect of the hormone upon odium stores independent of its action on sodium excretion

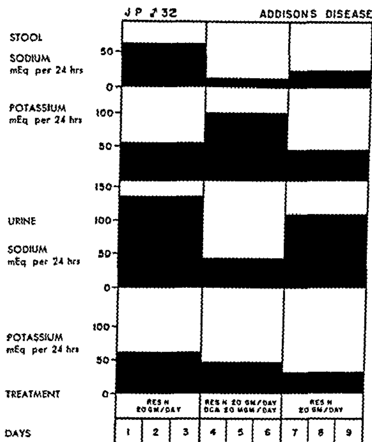
Other Actions Sayers[30] has demonstrated a weak action of DCA in inhibiting pituitary secretion of corticotropin This effect is not potent enough to be of pharmacologic significance in man, in the dosage usually employed in the regulation of Addison s disease i e 2 to 5 mg daily Although improved food intake and electrolyte regulation are the principal factors responsible for the alterations observed in carbohydrate metabolism in most patients with Addison s disease all available evidence points to the conclusion that DOC exhibits a minimal direct effect upon carbohydrate metabolism The administration of DOC does not induce eosinopenia and no cortisone-like effect upon inflammatory and allergic phenomena is observed

Patients with Addison s disease on long-continued DOC maintenance therapy despite an improved sense of well being and capacity to work usually exhibit one or all of the following metabolic abnormalities incapacity to tolerate prolonged fasting without hypoglycemic manifestations abnormal response to water load and persistence of the abnormal electroencephalographic pattern

Although it is widely recognized that DOC can produce a progestational endometrium in estrogen treated ovariectomized or immature animals [31] comparable effects have not been demonstrated in human subjects

Toxicity The undesirable side effects that may follow DOC overdosage are the direct result of an accentuation of the metabolic effect obtained with physiologic quantities of the hormone These include hypernatremia hypokalemia edema hypertension and cardiac enlargement [24] With intensive sodium retention and potassium depletion a significant intracellular exchange of sodium for potassium may occur Advanced intracellular potassium loss may eventually result in serious muscular weakness and even paralysis under these conditions morphologic lesions in cardiac muscle may be found [3] These changes can be effectively minimized by a

have demonstrated a definite measure of protection with DCA, 20 mg daily injected intramuscularly against the increased loss of sodium in the bowel caused by the oral administration of a cation exchange resin (Figure 2). It is possible that the gastrointestinal upsets observed so frequently in patients with untreated Addison's disease are intensified by a failure to reabsorb sodium and chloride effectively from the lumen of the bowel.



Amberlite XE96 cation exchange resin 1-2 mEq of potassium per gram

FIG 2 Excretion of sodium and potassium in a patient with Addison's disease. The patient was on a constant diet—240 mEq of sodium and 72 mEq of potassium. Stools and urine were collected in three-day pools and the values for sodium and potassium represent average daily excretion.

Body Cells During the administration of DCA to normal subjects or to patients exhibiting overt signs of adrenocortical insufficiency the expansion of extracellular fluid volume may well exceed the change in external water balance indicating a shift of water from intracellular to extracellular space [22-25]. A significant elevation of intracellular sodium and a decrease in intracellular potassium have also been frequently demonstrated during DCA administration to animals[26] and man [14, 27]. It appears probable that these changes in intracellular composition are largely dependent upon alterations

in the dosages ordinarily employed for clinical management, give rise to an increased excretion of urinary 17 ketosteroids However studies on ovariectomized and ovariectomized adrenalectomized primates have demonstrated the conversion of DOC to 17 ketosteroids [4]

Preparations It has long been recognized that the metabolic activity of steroid hormones can be significantly modified by esterification and by the physical state in which they are administered Miescher et al [41] originally demonstrated significant differences in the duration of effects exerted by the acetate palmitate and butyrate esters of DOC in oil solution For many years however the acetate of DOC has generally been employed for clinical use A significant advance in the administration of steroid hormones was achieved by the formulation by Deanesly and Parkes [42] of estrogenic and androgenic hormone tablets for subcutaneous implantation Thorn et al [44] subsequently standardized the maintenance treatment of patients with Addison s disease by the subcutaneous implantation of DCA pellets In addition both the intravenous and intraoral routes have been utilized for the administration of this hormone to patients with adrenocortical insufficiency

Six preparations of DOC are at present available for clinical use DCA in sesame or peanut oil for intramuscular injection DCA pellets for subcutaneous implantation DOC in propylene glycol for sublingual adminis tration DCA buccalets for intraoral absorption a microcrystalline aqueous suspension of DOC trimethylacetate for intramuscular injection and an aqueous solution of DOC glucoside designed for intravenous infusion

Desoxycorticosterone Acetate in Oil After its initial synthesis and isolation the acetate ester of DOC was promptly shown to be of therapeutic value in the management of both acute and chronic adrenocortical insufficiency [45,46] Administered by deep intramuscular injection DCA in sesame oil was thereafter widely employed for the maintenance therapy of patients with Addison s disease and subsequently for the standardization of daily hormone requirement prior to the implantation of pellets for long-term treatment The preparation is ordinarily administered once daily since the effects of a single intramuscular dose endure for approximately 24 hours The average daily dose used in the treatment of patients with Addison s disease is 1 to 3 mg a day [47] Larger doses of 5 mg or more may be required in unusual patients and in adrenal crisis

Desoxycorticosterone Acetate Pellets The maintenance therapy of patients with Addison s disease by the subcutaneous implantation of DCA pellets offers certain distinct advantages the provision of a more constant rate of hormone absorption reduction of the total hormone requirement owing to the efficiency of utilization resulting from continuous absorption and the avoidance of daily intramuscular injections During the past decade the administration of DCA by this technic has without doubt constituted the mainstay of substitution therapy in the majority of patients with chronic adrenocortical insufficiency and has been responsible in no small part for a significant reduction in the mortality of this disease [48]

restriction of sodium and chloride intake and the administration of supplementary potassium

In view of the potential importance of the adrenal cortex in the maintenance of experimental and essential hypertension[33,34] considerable interest has centered upon the capacity of excessive quantities of DCA to provoke hypertension in patients with Addison's disease[35] Furthermore, it has been noted that blood pressure may be restored to abnormally high levels by the administration of DCA to normotensive patients with Addison's disease who were afflicted with essential hypertension prior to the development of adrenal insufficiency[36] Although the administration of the hormone to patients with essential hypertension[34] has been reported to produce a significant rise in blood pressure this effect is quite unusual in normal subjects[35] The observation that prolonged administration of large quantities of DCA to patients with 'salt losing nephritis' causes no rise in blood pressure and in the absence of a sufficient intake of sodium chloride may be accompanied by actual hypotension indicates that this action of the hormone is in all likelihood dependent upon the intact kidney but does not distinguish between an effect upon sodium retention and a possible influence on the renal production of vasopressor substances

Absorption DCA is absorbed readily by the intramuscular or subcutaneous route and also by the mucous membranes of the mouth It differs from other adrenal steroids such as corticosterone cortisone and hydrocortisone, in being relatively ineffective when administered orally Kuizenga and Nelson[47] have shown in rats that DCA is one thirty fifth as effective orally as parenterally and that it is destroyed locally in the gastrointestinal tract This finding is in agreement with clinical experience[38] Investigations of the percutaneous and rectal routes of administration in patients with Addison's disease demonstrated absorption to be poor

Intermediary Metabolism and Excretion Little is known of the metabolic processes involved in the degradation and transformation of DOC Hechter et al[4] reported that the perfusion of this hormone through beef adrenal glands gave rise to the formation of corticosterone (compound B) Recent studies by Schneider[39] on the incubation of DOC with surviving rat liver slices have demonstrated a rapid disappearance of the conjugated unsaturated system (3 keto-Δ^4 structure) Four allopregnane derivatives three of which possess a hydroxyl group at carbon 3 were isolated It is of interest that bioassay of the ketonic fraction indicated that approximately 3 per cent of the incubated DOC had been converted to androgenic material

Although none of the metabolites isolated by Schneider have been shown to be excretory products of DOC there is sufficient evidence that the hormone is excreted at least in part as pregnanediol Horwitt et al[40] have demonstrated pregnanediol excretion after the oral administration of DCA to 2 male and 1 female patient with Addison's disease and to 1 male subject with hypogonadism Similarly Cuyler et al[41] were able to demonstrate this transformation in healthy men

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The administration of DCA to patients with Addison's disease does not

acetate in isotonic saline solution, containing methyl cellulose and Tween 20 as suspending agents. An average crystal size of 50 microns ensures a freely injectable suspension. Balance studies have revealed maximal sodium and chloride retention within 48 hours of injection (Figure 3). The average period of effective electrolyte regulation resulting from a single intramuscular injection in patients with adrenocortical insufficiency is five or six weeks. Approximately one thirtieth to one-fiftieth of the injected dose

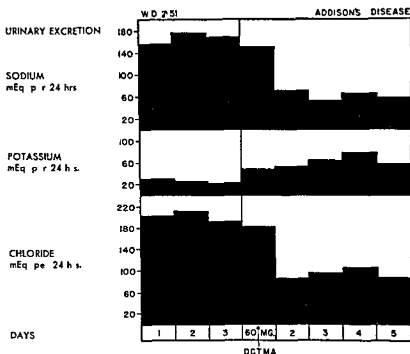


FIG 3 Effect of desoxycorticosterone trimethylacetate upon electrolyte excretion. The patient was on a constant diet that included 146 mEq of sodium and 64 mEq of potassium. The trimethylacetate of desoxycorticosterone (DCTMA) was given as a single intramuscular injection

is absorbed daily. Therefore the administration of a single 30 mg dose provides a daily absorption of approximately 0 6 to 0 8 mg. The injections are conveniently administered at monthly intervals to insure sufficient overlap of metabolic effects to avert all evidences of inadequate hormonal control. The advantages of this technic of DOC administration are as follows: infrequent injections, avoidance of the minor surgical procedure involved in pellet implantation, flexibility of dosage schedules, and constancy of control especially in comparison to the terminal period of pellet therapy during which the symptoms of adrenal insufficiency appear comparatively often.

Desoxycorticosterone Glucoside. Originally prepared by Miescher et al.[57] DOC glucoside is considerably more water soluble than either free DOC or the acetate ester. The material is available as a 1 per cent solution in

Two pellet preparations are currently available one containing approximately 125 mg and the other 75 mg of hormone Pellets containing 125 mg of DCA are absorbed at a rate of approximately 0 3 to 0 4 mg per day which is equivalent in terms of metabolic effect to the daily intramuscular injection of approximately 0 5 mg of the hormone in oil solution[49] It is apparent that the continuous absorption of hormone provided by subcutaneous pellets is approximately 25 per cent more efficient than that resulting from intermittent intramuscular injection One pellet therefore may be considered equivalent to a daily dose of 0 1 cc of the standard preparations of DCA in oil Pellets containing 75 mg of hormone are absorbed at a rate of approximately 0 21 mg a day[50] and are equivalent to approximately 0 05 cc of the oil solution injected daily

The number of pellets required for optimal maintenance therapy is established on the basis of the daily requirement of DCA in oil administered by intramuscular injection The duration of effective electrolyte control achieved during substitution therapy by pellet implantation is approximately 8 to 12 months This method of hormone administration therefore produces the longest therapeutic action of the preparations of DCA currently available for clinical use The technic of pellet implantation has been adequately described elsewhere[48]

Sublingual and Intraoral Preparations of Desoxycorticosterone Acetate The administration of DCA by the sublingual and intraoral routes has been advocated by Anderson et al[50] The sublingual preparation was administered in droplet form the hormone being dissolved in propylene glycol and alcohol Early studies with this preparation[38] demonstrated that approximately 5 mg of the hormone administered sublingually in divided doses throughout the day was required to produce a metabolic effect equivalent to that resulting from the daily absorption of 1 mg of DCA from subcutaneous pellets The necessity for frequent administration the objectionable taste experienced by some patients and a tendency to precipitate on cooling or exposure to air have largely resulted in the replacement of sublingual drops by the intraoral tablet or buccalet which available as hard compressed tablets containing 2 mg of DCA in a propylene glycol–wax base is placed either in the buccal pouch or beneath the tongue for direct absorption through the oral mucous membrane The average hormone dose reported by Anderson et al[51] was 4 8 mg a day ordinarily administered in divided doses It is to be emphasized that the administration of DCA by this route does not provide adequate treatment for patients in adrenal crisis

Microcrystalline Suspension of Desoxycorticosterone Trimethylacetate Recently the trimethylacetate ester of DOC originally prepared by Wieland et al,[52] has been demonstrated to produce a protracted metabolic effect in man[53] and animals[54,55] after the intramuscular administration of a single dose An extensive clinical trial in patients with Addison's disease has confirmed these observations and established the usefulness of this preparation in substitution therapy[56] The preparation employed, soon to be available for general use, is a microcrystalline suspension of DOC trimethyl

acetate in isotonic saline solution containing methyl cellulose and Tween 20 as suspending agents An average crystal size of 50 microns ensures a freely injectable suspension Balance studies have revealed maximal sodium and chloride retention within 48 hours of injection (Figure 3) The average period of effective electrolyte regulation resulting from a single intramuscular injection in patients with adrenocortical insufficiency is five or six weeks Approximately one thirtieth to one fiftieth of the injected dose

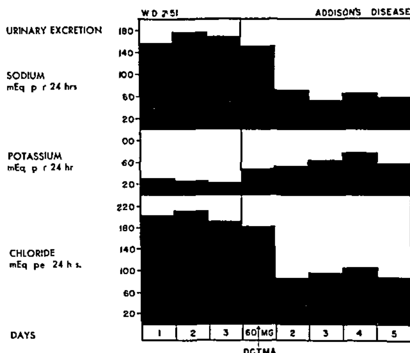


FIG 3 Effect of desoxycorticosterone trimethylacetate upon electrolyte excretion The patient was on a constant diet that included 146 mEq of sodium and 64 mEq of potassium The trimethylacetate of desoxycorticosterone (DCTMA) was given as a single intramuscular injection

is absorbed daily Therefore the administration of a single 30 mg dose provides a daily absorption of approximately 0 6 to 0 8 mg The injections are conveniently administered at monthly intervals to insure sufficient overlap of metabolic effects to avert all evidences of inadequate hormonal control The advantages of this technic of DOC administration are as follows infrequent injections avoidance of the minor surgical procedure involved in pellet implantation flexibility of dosage schedules and constancy of control especially in comparison to the terminal period of pellet therapy during which the symptoms of adrenal insufficiency appear comparatively often

Desoxycorticosterone Glucoside Originally prepared by Miescher et al [57] DOC glucoside is considerably more water soluble than either free DOC or the acetate ester The material is available as a 1 per cent solution in

10 per cent glucose containing 10 per cent acetamide for stabilization and has been chiefly employed for intravenous administration. Comparative studies in animals have demonstrated that the water soluble glucoside produces a more rapid onset of action and a more transient effect than the oil solution of DCA.[58] Swingle[59] has found that the intravenous administration of DOC glucoside in doses of 300 mg. is capable of reviving adrenalectomized dogs from severe adrenal insufficiency even when no supplementary therapy is employed.

Administration of this preparation to human subjects by intramuscular injection[60] and intravenous infusion[61] resulted in sodium and chloride retention. In addition, an increase in water excretion and a decrease in the tubular reabsorption of glucose during the period of hormone infusion have been described. The DOC glucoside has been little used in this country in the treatment of adrenal crisis. Foreign reports[62] indicate, however, that intravenous administration of 100 to 300 mg. of the glucoside preparation is beneficial. In our experience the effect of these large doses on electrolyte excretion is not significantly greater than that obtained from the daily intramuscular injection of 15 to 20 mg. of DCA in oil.

Clinical Uses of Desoxycorticosterone. The value of DOC in the treatment of Addison's disease is well established. With measurements of body weight, hematocrit, blood pressure, and heart size as guides to dosage, the optimal hormone requirement is determined by the daily intramuscular injection of DCA in oil. When dosage has been firmly established at a constant level, treatment may be continued with a long acting DOC preparation.

When subcutaneous pellets are employed for long term maintenance therapy, the following dosage equivalents may be employed. For each 0.5 mg. of DCA in oil injected daily, one pellet of 125 mg. may be substituted; alternatively, for 0.3 mg. of the oil solution injected daily, one 75-mg. pellet may be implanted. Ordinarily, when more than four pellets are required, one less than the calculated number should be employed to avoid overdosage. The number of pellets implanted in a series of 180 patients with Addison's disease seen in this clinic ranged from one to eight per patient, the average requirement varied between two and four pellets per implantation.

The alternative method of maintenance treatment is the intramuscular injection of DOC trimethylacetate. Dosage is determined in the manner described for pellet implantation, and for each milligram of DCA injected daily, 30 milligrams of the microcrystalline suspension is administered at approximately 30-day intervals. Although the quantity of hormone absorbed each day from the depot of long acting material is actually somewhat less than that provided by daily injection of DCA in oil, the efficiency of constant hormone absorption enhances the ultimate metabolic effect derived from the trimethylacetate ester in the same manner described for subcutaneous pellets. Dosages employed in a series of 60 patients with Addison's disease recently treated with this preparation ranged from 15 to 90 mg. a month, with an average requirement of 30 to 60 mg. One may most easily determine the adequacy of the dose by following the patient's weight (Figure 4). In our

opinion, this technic of DOC administration currently constitutes the method of choice for long term maintenance therapy

Along with cortisone DOC has also been employed as replacement therapy in patients who have undergone complete bilateral adrenalectomy for hypertension or for reactivated carcinoma of the prostate with metastases[83] In

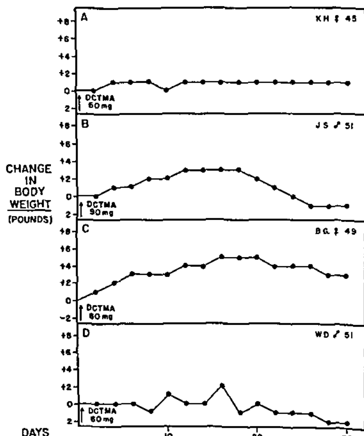


FIG 4 Weight curves in patients with Addison's disease treated with desoxycorticosterone trimethylacetate (DCTMA) A = no weight change—satisfactory dose B = typical weight chart with slight weight gain in the middle of the period—satisfactory dose C = excessive weight gain with edema—overdosage D = weight loss toward the end of the period indicating underdosage

the former group an attempt is made to obtain adequate regulation with cortisone and supplementary salt In some cases however the administration of minimal quantities of DOC is essential for the maintenance of electrolyte balance Whereas from a theoretic point of view DOC therapy is contraindicated in the treatment of patients with hypertensive vascular disease after complete adrenalectomy this is not true in the management of post adrenalectomy prostatic cancer since the quantities of DOC employed in the clinical regulation of electrolyte metabolism lead to no detectable increase in the urinary excretion of substances with androgenic activity

Advantage has been taken of certain of the physiologic actions of DOC in attempts to modify other clinical conditions. The observation that the administration of DCA to normal rats raises the threshold of response to electroconvulsive treatment[64] has led to the use of this hormone in patients with epilepsy.[65,66] In some cases a decrease in the frequency and severity of attacks has been noted. Because of certain striking similarities between adrenal crisis and traumatic shock,[67] DOC has undergone extensive clinical and experimental trials in the treatment of the latter syndrome. The results obtained have been conflicting and exceedingly variable.[68] In view of its potential effects upon blood pressure, the hormone has been tried as an adjunct in the therapy of patients with syncopal attacks associated with orthostatic hypotension. Continued treatment has resulted in an appreciable rise in both systolic and diastolic blood pressure and a definite amelioration of the syncopal episodes, although a measurable fall in pressure still occurred in the upright position.[23] Because of possible extrarenal effects on the internal distribution of electrolytes, DOC has been administered to hyperkalemic patients with lower nephron nephrosis without demonstrable benefit.[69] In the light of recent studies on the regulatory effect of adrenal hormones upon gastrointestinal absorption of electrolytes, the possibility of employing DOC in patients with diarrheal diseases should be explored.

Experience to date indicates that DOC is ineffective in the treatment of diseases associated with inflammatory or allergic reactions.

Corticosterone (Compound B)

The presence of corticosterone, or compound B of Kendall, in relatively high concentration in adrenocortical extracts has long been recognized.[70,71] Recently, its significance has been emphasized by the studies of Hechter et al,[4] who have shown that corticosterone and 17-hydroxycorticosterone (hydrocortisone) are the principal steroid substances obtained by perfusion of the isolated bovine adrenal gland with corticotropin. The synthesis of corticosterone from a pregnanediol derivative has been achieved[72] and sufficient material has been made available for study to allow a preliminary evaluation of its clinical as well as its physiologic effects.

Physiologic Actions. As might be anticipated from its chemical structure, corticosterone possesses, qualitatively, the electrolyte-regulating activity of DOC as well as some of the potentialities of the carbohydrate-regulating hormones (cortisone and hydrocortisone).

In 1940 Thorn et al[73] gave by intramuscular injection 80 mg. of corticosterone, isolated from adrenocortical extract by Kendall, to a patient with Addison's disease and noted an increase in fasting blood sugar, a depression in nonprotein respiratory quotient (R. Q.) and increased resistance to hypoglycemia. In the same year Ferrebee and his co-workers[74] reported little significant effect upon either carbohydrate metabolism or electrolyte excretion in a patient with Addison's disease who was given 90 mg. of corticosterone; however, the steroid was given in divided dose over a five-day period

concomitantly with the continued administration of a maintenance dose of DCA

Only recently with more liberal supplies of corticosterone available has further study been possible In 1951 Conn and his collaborators[75 76] reported their studies on corticosterone given to normal subjects and to patients with Addison s disease They were able to demonstrate quite marked sodium-retaining properties In Addison s disease the daily injection of 25 mg of the steroid produced sodium retention more marked than that induced by the combined intramuscular administration of 20 mg of cortisone acetate and

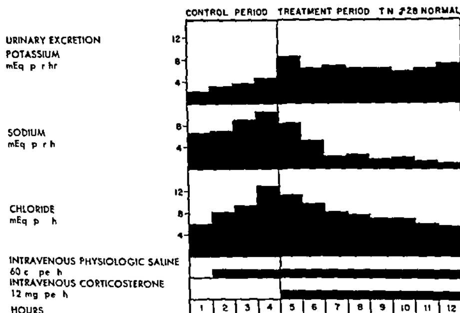


FIG 5 Effects of intravenous injection of corticosterone upon electrolyte excretion The patient was fasting throughout the experiment

2 mg of DCA daily similarly in a normal subject 200 mg of corticosterone proved more effective than an equivalent dose of cortisone acetate The renal excretion of potassium was increased in patients with Addison s disease and in 1 of 2 normal subjects studied The associated increase in body weight and decrease in hematocrit were similar to the changes seen with sodium retention induced by DOC During continued administration to normal subjects an escape from sodium and chloride retention similar to that frequently observed with DOC occurred In both normal subjects and patients with Addison s disease corticosterone led to decreased carbohydrate tolerance greater resistance to insulin and elevation of fasting blood sugar As with the electrolyte changes much larger doses were required to produce these phenomena in normal subjects than in patients with Addison s disease Furthermore the effects upon carbohydrate metabolism were considerably less striking than those upon electrolyte metabolism

Our findings in normal subjects in patients previously subjected to complete bilateral adrenalectomy and in patients with Addison's disease treated with corticosterone are similar to those of Conn et al and may be summarized as follows

Desoxycorticosterone Effects The effects of corticosterone upon the renal excretion of electrolytes are well illustrated in Figure 5 It is apparent that the intravenous administration of corticosterone (free alcohol) to a normal subject at a rate of 12 mg per hour over an eight hour period resulted in marked sodium and chloride retention with increased potassium excretion The changes in sodium and potassium excretion became evident within an hour or two of the beginning of hormone infusion were approximately simultaneous in onset and rapidly attained a maximal level

The intramuscular administration of corticosterone to patients with adrenocortical insufficiency in doses of approximately 50 mg a day causes retention of urinary sodium and chloride promotes urinary potassium excretion and lowers the ratio of sodium to potassium in saliva The e effects appear to be approximately equal to those produced by the daily injection of 1 or 2 mg of DCA It is evident that milligram for milligram corticosterone is more potent than cortisone in the regulation of electrolyte excretion Although these effects of corticosterone are more pronounced with intramuscular injection than with oral administration Figure 6 demonstrates that significant changes in electrolyte excretion can be produced by large doses of the hormone given by mouth

The DOC like qualities of the steroid are further illustrated by the effects of corticosterone after complete bilateral adrenalectomy in a patient with hypertension The administration of 50 to 100 mg of free corticosterone by mouth and subsequently by injection produced a recurrence of headache weight gain a significant elevation of blood pressure and an increase in cardiac size

Cortisone like Effects The administration of 50 to 100 mg of corticosterone daily improves the response of patients with Addison s disease to hypoglycemia induced by insulin injection or prolonged fasting It is of interest however that the rise in total nitrogen excretion obtained is minimal even with doses as large as 300 mg a day (Figure 6)

Corticosterone has been shown to be capable of restoring to normal the characteristically slow electroencephalogram (EEG) encountered in untreated or DOC treated patients with Addison s disease As might be expected from this finding patients with Addison s disease may experience a definite increase in sense of well being during corticosterone treatment On the other hand in doses up to 300 mg a day corticosterone has produced no significant change in the level of circulating eosinophils and is considerably less effective than cortisone in restoring to normal the impaired capacity of the patient with Addison's disease to excrete an ingested water load (Figure 7) No evidence of an effect upon inflammatory or allergic processes has been reported

Toxicity No toxic effects of corticosterone have been described other than those that may be considered to be an exaggeration of its physiologic action through overdosage Because of the relatively potent salt retaining effect of this compound in relation to its carbohydrate-regulating capacity

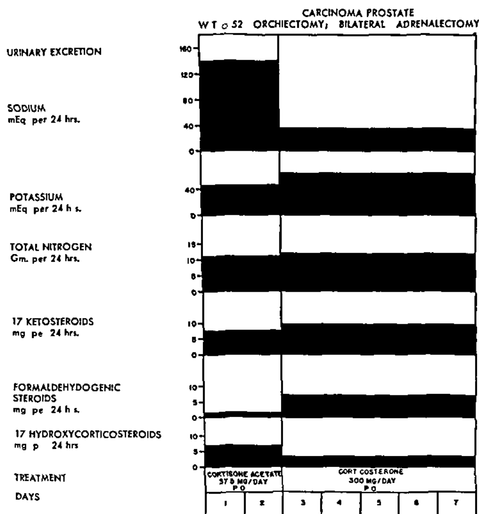


Fig 6 Metabolic studies on the effect of the oral administration of corticosterone The patient was on a con tant diet (odium 141 mEq and potassium 84 mEq) All values shown repre ent mean daily excretions (The increase in 17 ketosteroids and formaldehydogenic steroids is to be contrasted with the decrease in 17 hydroxycorticosteroids)

excessive salt and water retention may be observed in patients with Addison s disease even though dosage is inadequate for satisfactory regulation of the electroencephalographic abnormality the disturbance in water turnover and the tendency to fasting hypoglycemia

Absorption and Fate There is little knowledge concerning the mode of absorption of corticosterone Physiologic activity after oral and intramuscular administration shows that absorption occurs by either route, but quantitative data are lacking

Although 17-ketosteroids continue to be detectable in the urine of patients with Addison's disease maintained on corticosterone, this substance seems to be much less active as a precursor of 17-ketosteroids than either cortisone or hydrocortisone This is illustrated by the striking differences in

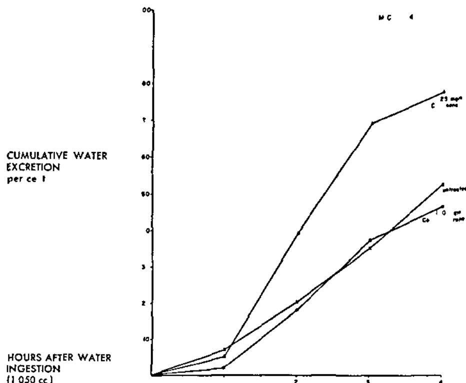


Fig 7 Comparative effects of corticosterone and cortisone upon the water test in Addison's disease Water excretion is expressed as per cent of water ingested

ketosteroid excretion *of a patient with carcinoma of the prostate previously* subjected to bilateral orchiectomy and total adrenalectomy During a five-day period in which he was given 300 mg of free corticosterone daily by mouth, 11 6 mg a day was the highest level of ketosteroid excretion attained and the mean output for the period was 9 8 mg a day (Figure 6) In contrast with 300 mg of oral hydrocortisone acetate (equivalent to 282 mg of free hydrocortisone daily) urinary ketosteroids reached the impressive figure of 47 2 mg a day, the values obtained during cortisone administration were intermediate Similarly, measurement of the biologic androgenic activity of the urine in the same patient indicated that corticosterone was a much less effective precursor than either cortisone or hydrocortisone [77] although the absolute values for all three compounds were relatively low Studies carried out by Wolfson et al [78] have demonstrated still another difference in the

urinary and products derived from these hormones. A significant rise in urinary steroids detectable by the Pettenkofer colorimetric reaction (acid furfural) was produced by the administration of corticosterone but not by cortisone or hydrocortisone. Since adrenal activation with corticotropin also causes a rise in urinary Pettenkofer chromogens these studies were considered to provide additional evidence that corticosterone is a primary secretory product of the adrenal cortex.

Excretion of formaldehydogenic steroids in patients with adrenal insufficiency receiving maintenance doses of corticosterone appears to be the same as that seen in patients receiving cortisone. It is of interest to note, on the other hand, that the urinary excretion of total 17-hydroxycorticosteroids is not increased (Figure 6). Since the latter procedure[79] measures chiefly corticosterone derivatives possessing a hydroxyl function at C-17, it is evident that administered corticosterone does not undergo a significant degree of 17-hydroxylation. This is in agreement with the results of adrenal perfusion *in vitro*.[4]

Preparations and Dosage. At present limited amounts of free corticosterone are available for investigational use only in tablets for oral administration and in a saline suspension for intramuscular injection. In the maintenance of patients with adrenal insufficiency the daily dose of corticosterone appears to be approximately 25 to 50 mg. by intramuscular injection or 50 to 100 mg. by mouth.

Clinical Uses. The clinical usefulness of corticosterone appears at present to lie principally in its potentialities as replacement treatment for patients with adrenocortical insufficiency. A few clinical trials have shown it to possess no antirheumatic activity.[80]

Limited experience in this clinic supports Conn's impression that corticosterone may prove satisfactory as the sole adrenal replacement in patients with Addison's disease. A 33 year old man with Addison's disease of two years' duration has been well maintained for four months on no treatment other than corticosterone, first intramuscularly and then by mouth. It was found that 50 mg. by injection was sufficient for maintenance of weight and electrolyte balance but that 100 mg. by mouth was required to maintain the same beneficial effect. This is in accord with Conn's finding that intramuscular injection of corticosterone is two to three times as effective as the oral form. The patient's EEG is normal; his feeling of well being equals that which he experienced on 25 mg. of cortisone daily. A mild crisis precipitated by a respiratory infection was satisfactorily controlled with no hormonal treatment other than 200 mg. of corticosterone intramuscularly.

A 44 year old woman with Addison's disease has been treated with corticosterone alone for two months; she has not fared as well, however, as the patient just described. On 100 mg. of corticosterone daily by mouth she suffered from excessive salt retention which required reduction of the dose to 50 and then to 35 mg. a day. At these levels of dosage she is free of edema but lacks a sense of well being comparable to that produced by 25 mg. of cortisone acetate daily.

Thus our preliminary impression is that corticosterone which combines the therapeutic properties of DOC and cortisone in a preparation active by mouth may be satisfactory as the sole maintenance treatment for some patients with Addison's disease On the other hand the same combination of properties may be a disadvantage in patients who prove to be more sensitive to the salt retaining than to the carbohydrate regulating properties of the hormone Cortisone and DOC given separately and therefore independently variable appear to provide a more flexible method of controlling the requirements of patients with Addison's disease

The relatively small increase in urinary output of 17 ketosteroids after oral administration of corticosterone is accomplished by only a moderate increase in metabolic products with androgenic activity Corticosterone may therefore have a place in the specialized problem of the maintenance of the patient with carcinoma of the prostate who has undergone orchiectomy and adrenalectomy for the purpose of reducing the level of androgen production It is also possible that corticosterone will act as a satisfactory inhibitor of the normal adrenal cortex in patients with cancer of the prostate or breast

Few data are available so far on the effectiveness of corticosterone as an inhibitor of adrenocortical activity in the abnormally active adrenal gland Wilkins et al [81] have recently compared the effects of corticosterone and of cortisone upon electrolyte regulation in a 1 year old girl with adrenogenital syndrome and accompanying adrenal insufficiency Adrenal suppression as judged by urinary 17 ketosteroid excretion was more complete with cortisone than with corticosterone which however had a definite effect On the other hand corticosterone in this patient was more potent than cortisone in causing sodium retention

Compound A (11-Dehydrocorticosterone)

The history of compound A is similar to that of corticosterone Dehydrocorticosterone was the first adrenocortical hormone with carbohydrate-regulating activity to be produced in quantities allowing adequate clinical *investigation* [82] Early *studies*[83,84] *indicated that compound A* like corticosterone possessed both electrolyte regulating and carbohydrate-regulating effects Both actions were more easily demonstrated in patients with Addison s disease than in normal subjects [85]

The intramuscular injection of 40 to 100 mg of compound A to patients with Addison s disease produced moderate salt and water retention, weight gain a rise in blood pressure and an increase in cardiac size Changes in intermediary metabolism were less prominent, although small increases were observed in the excretion of urinary nitrogen potassium phosphorus and uric acid The effects of the steroid upon glucose and insulin tolerance were variable but the occurrence of hypoglycemic symptoms during prolonged fasting was successfully prevented

The therapeutic uses of compound A appear to be the same as those of corticosterone

Compound S

Reichstein and Von Euw were the first to isolate 11-desoxy 17 hydroxy corticosterone or compound S from beef adrenal glands in 1938 In 1940 the same workers accomplished its synthesis [86]

In its physiologic action compound S behaves like DOC [54] Clinton and Thorn[87] observed a moderate decrease in urinary sodium and chloride in a dog given 25 mg of compound S by intramuscular injection In 2 normal human subjects given 400 mg of compound S acetate daily by mouth for five days and 200 mg of the hormone intramuscularly for five days respectively no changes in urinary sodium potassium or chloride were noted [88] Similar findings were obtained by Terry and London [89] Pearson et al [90] on the other hand observed a slight retention of sodium chloride in 4 patients with chronic lymphatic leukemia who were given 200 mg of compound S acetate daily for 10 to 24 days We obtained similar results in a patient who had undergone orchiectomy and bilateral adrenalectomy for metastatic carcinoma of the prostate and received 300 mg of the hormone by mouth daily for four days Compound S had no effect upon calcium and phosphorus excretion [90]

In doses up to 400 mg a day both by intramuscular and by oral administration in the human being compound S acetate appeared to have no influence on organic metabolism as measured by intravenous glucose tolerance tests and changes in serum total lipid and cholesterol and urine glucose uric acid creatinine and total nitrogen [88 90]

Compound S exhibited a weak corticotropin suppressing activity in the rat [54] The hormone showed no effect upon the response of adrenalectomized rats to water loading [54] No eosinophil response followed either the oral or the intramuscular administration of compound S acetate to man [88 89] In contrast to cortisone and hydrocortisone this hormone was without effect upon the lymphatic tissue of patients with chronic lymphatic leukemia [90]

That compound S may be absorbed from the gastrointestinal tract is indicated by the rise in urinary 17 ketosteroids that occurs when the hormone is given by the oral route [89] Fajans et al [88] however found no increase in urinary 17 ketosteroids when the hormone was administered by intramuscular injection to a normal man in a dose of 200 mg daily for five days In neither case was there any appreciable rise in urinary formaldehydogenic steroids Polley and Mason [91] however found slight increases in the urine of both 17 ketosteroids and formaldehydogenic steroids after the intramuscular administration of 200 mg of compound S acetate daily for seven days to a patient with rheumatoid arthritis We have observed a considerable rise in the urinary excretion of 17 hydroxycorticosteroids in the patient who underwent orchiectomy and bilateral adrenalectomy for metastatic carcinoma of the prostate and received 300 mg of compound S acetate by mouth daily for four days Hechter et al [4] reported that the perfusion of compound S through beef adrenal glands caused the formation of 17 hydroxycorticosterone (compound F)

Compound S acetate has been found to be without effect in rheumatoid arthritis[91] and chronic lymphatic leukemia.[90] No instances of its use in other diseases have been reported.

Cortisone

Cortisone was first isolated from adrenocortical extracts in 1936 almost simultaneously in the laboratories of Kendall,[79] Reichstein,[8] and Wintersteiner.[92] Although at the dosage levels originally employed the drug was nearly devoid of activity in the maintenance of life in adrenalectomized animals, the demonstration by Mason et al.[79] of the effectiveness of cortisone in the muscle work test of Ingle[94] actually constituted the first evidence of physiologic action in a crystalline steroid of adrenal origin. The partial synthesis of cortisone from desoxycholic acid was eventually accomplished in 1946 by Sarett,[95] employing methods extending the procedures developed chiefly by Reichstein[96] and Kendall.[97] Subsequent improvements in the synthetic process made possible the production of cortisone in quantities sufficient for clinical trial by 1948. Thus 20 years after the initial preparation of effective adrenocortical extracts, the isolation, chemical characterization, partial synthesis, and finally large-scale production of this highly active steroid hormone were accomplished. Recent advances in this remarkably complex field include the complete synthesis of cortisone[98] and the utilization of microorganisms for enzymatic oxygenation at C-11.[99] The latter ingenious procedure has been successfully adapted for large scale production.

The immediate application of cortisone followed two general lines of investigation: an analysis of its important metabolic effects and its efficacy as substitution therapy in patients with chronic adrenocortical insufficiency,[100, 101] and an exploration of its possible usefulness in the treatment of rheumatoid arthritis[102] and other inflammatory diseases.[103] These studies have provided a considerable knowledge of the physiologic effects of cortisone in man, but have as yet given little insight into the precise mechanisms by which these effects are produced. It seems inevitable, however, that an eventual understanding of the divers influences exerted by cortisone on a wide variety of diseases depends upon the successful delineation of the fundamental actions (or action) that the hormone exerts on the mechanisms of cellular metabolism. Although this ideal is admittedly distant, it is quite apparent that the advent of cortisone as a therapeutic agent of striking, even dramatic, consequences has already contributed significantly to the study of metabolic processes on the one hand and of pathologic processes on the other.

Physiologic Actions

The physiologic actions of cortisone may be discussed conveniently under four headings: the influence of this hormone on intermediary metabolism, its effects upon specific tissues, its influence on growth, and its effects upon mechanisms of defense.

Intermediary Metabolism. *Organic Metabolism*

CARBOHYDRATE METABOLISM. The classic experiment of Long, Katzin, and Fry[104] showed that adrenal insufficiency in animals is characterized by

low blood glucose levels during fasting depletion of liver but not muscle glycogen decreased excretion of urinary nitrogen high standard R Q , and increased sensitivity to insulin Similar findings in patients with Addison's disease were reported by Thorn et al [73] In both instances the metabolic disturbances could be reversed by the administration of cortisone

There is little doubt that the influence of cortisone on carbohydrate metabolism may be explained in part by its ability to stimulate gluconeogenesis from protein This is indicated by the coexistence of increased excretion of urinary nitrogen and increased glycogen stores in animals and human beings after cortisone administration Further support for the view that this hormone influences gluconeogenesis has recently been provided by Welt et al ,[10] who showed that cortisone fed rats given a constant infusion of C^{14} labeled glucose increased liver glycogen from some source other than body glucose That cortisone may accelerate gluconeogenesis from fat has been suggested by Kinsell et al [106] who demonstrated that in diabetic patients maintained on carbohydrate-free diets the hormone may produce a degree of glycosuria in excess of that readily explicable on the basis of gluconeogenesis from protein alone It is of interest in this connection to note the wide discrepancy between nitrogen excretion and blood sugar level resulting from the intravenous infusion of cortisone over an eight hour period in a normal fasting subject (Figure 8)

In addition to its effect upon the stimulation of gluconeogenesis it has been felt[107] that cortisone must inhibit some phase of carbohydrate utilization (storage as glycogen oxidation to carbon dioxide and water or conversion to fat and protein) This view has been supported by the following evidence the observation that cortisone will cause a fall in the R Q in animals[104] and human beings [73] the finding that cortisone suppresses the tolerance of the eviscerated rat for intravenously administered glucose [108] and the observation that there is a decreased conversion of carbohydrate to fat in the cortisone fed intact animal [109] It is not clear whether the inhibitory effect of cortisone upon carbohydrate utilization is exerted at the initial reaction involved in glucose uptake by tissues i e the hexokinase reaction or at some other point in the metabolic pathway of glucose That the hormone may inhibit the conversion of carbohydrate to fat at a point other than the hexokinase reaction has been indicated by the observation of Brady et al [110] that the incorporation of C^{14} labeled acetate by rat liver slices into long chain fatty acids is inhibited by the previous injection of cortisone

In a discussion of the influence of cortisone on carbohydrate metabolism the relation of this hormone to diabetes mellitus is of particular interest Long and Lukens[111] were the first to show conclusively that adrenalectomy decreases the severity of pancreatic diabetes Glycosuria is diminished and there is a marked increase in insulin sensitivity That this is also true in man has been demonstrated in patients with coexisting Addison s disease and diabetes mellitus [11, 113] The onset of adrenal insufficiency in diabetic patients is marked by a decreasing insulin requirement and by an increased tendency to hypoglycemic reactions of unusual severity in addition to the usual symp

toms of Addison's disease On the other hand Long et al [104] observed in 1940 that the glycosuria of the partially depancreatized rat could be intensified by cortisone Shortly thereafter Ingle[114] reported the production of glycosuria in force fed normal animals by the administration of cortisone Of particular interest to the clinician are the more recent observations made in both normal subjects and diabetic patients during the administration of cortisone or

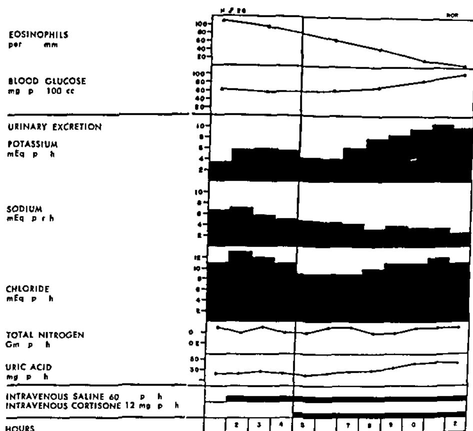


FIG 8 Result of intravenous cortisone infusion in a normal subject The patient was fasting throughout the experiment All urinary analyses were performed on one hour collections

corticotropin Conn and his collaborators[115] have shown that the administration of corticotropin in doses of 75 to 150 mg daily for 5 to 10 days may produce in normal subjects fasting hyperglycemia glycosuria and diminished tolerance to carbohydrate The clinical diabetes thus produced was further characterized by a renal component of glycosuria by a marked degree of insensitivity to insulin and by its complete reversibility upon discontinuance of hormone administration Although Conn's observations have been confirmed by a number of investigators the general opinion has been that such marked diabetic responses are the exception rather than the rule in normal subjects or patients who show no evidence of preexisting diabetes For example in a series of 27 patients with rheumatoid arthritis Sprague

et al [116] found that the prolonged administration of cortisone in doses of 100 to 200 mg daily caused light and inconsistent increases in fasting blood glucose and decreased glucose tolerance of a mild degree in only 4 patients Similar findings have been reported by Wilson and his associates [117] who concluded that the functional reserve of the pancreatic islets is usually sufficient in normal subjects to compensate for the diabetogenic action of cortisone

PROTEIN METABOLISM Fasting adrenalectomized animals and patients with Addison s disease[73] exhibit a decreased urinary nitrogen excretion that can be reversed by the administration of cortisone In addition it has been repeatedly shown that large doses of cortisone in the intact organism will lead to a negative nitrogen balance It should be emphasized however that this response may be diminished by the feeding of high carbohydrate or high protein diets and by the administration of supplementary potassium [118] The precise mechanisms by which cortisone increases urinary nitrogen excretion are not clearly understood Hoberman [119] in studies of the effect of cortisone administration upon the fate of injected isotopic glycine in adrenalectomized animals reported both a stimulation of protein catabolism and an inhibition of anabolism The latter observation supports the hypothesis first proposed by Albright [120] Hoberman was unable to detect any abnormality in amino acid catabolism in adrenalectomized rats The finding of a lessened accumulation of amino acids in the plasma of hepatectomized adrenalectomized rats[121] likewise emphasizes the antianabolic action of the 11 17 oxysteroids such as cortisone The observation[122] that cortisone will restore to normal the diminished activity of liver amino acid oxidase in adrenalectomized animals indicates however that this hormone may act in part at the amino acid level of nitrogen metabolism

After intense stimulation of the adrenal cortex in man there is a greatly increased urinary excretion of histidine glutamine alanine threonine glycine serine lysine and small increases in glutamic and aspartic acids cystine and methionine [123] The associated rise in serum amino acid nitrogen indicates that the hormone action is not limited to its effect upon renal threshold [124] The increase in urinary cystine and methionine accounts for only 50 per cent of the increase in urinary organic sulfur [125] After corticotropin administration in man there is also a rise in the urinary total sulfate which may result in part from an increased urinary output of sulfuric acid conjugates of adrenal steroids

Little is known of the influence of cortisone on purine and pyrimidine metabolism It has been shown however that the administration of this hormone to normal human beings[116] and to patients with Addison s disease[7] leads to an increased urinary excretion of uric acid (Figure 8) In some subjects little change in serum uric acid level was noted suggesting an increase in urate formation or mobilization Studies with isotopic uric acid in a patient with gout[126] indicated that the effect of 11 17-oxysteroids such as cortisone upon uric acid metabolism is predominantly one of increased renal clearance rather than increased production

LIPID METABOLISM Studies of the influence of cortisone on lipid metabolism have been meager and their interpretation difficult Levin and Farber[11] showed that the livers of fasting adrenalectomized rats contained considerably smaller quantities of neutral fat than those of intact animals, pretreatment with cortisone prevented this disturbance The administration of large doses of cortisone was found to cause intense lipemia and fatty livers in intact rabbits[1 8] and slight increases in neutral fat in the livers of normal rats[1 7] These observations have been interpreted in the past as indicating a low rate of fat mobilization and catabolism in the adrenalectomized animal that can be reversed by cortisone Stoerk and Porter,[129] however found that partially starved adrenalectomized rats showed less neutral fat in both liver and carcass than did intact animals on isocaloric diets This finding of a low body fat in adrenalectomized animals must indicate either a diminished liponeogenesis or an increased catabolism of fat Welt and Wilhelmi[109] from a study of the uptake of deuterium into liver and carcass fat by adrenalectomized rats on high carbohydrate fat free diets, concluded that adrenalectomy was followed by an increased rate of lipogenesis from carbohydrate Thus it seems that there is increased fat catabolism after adrenalectomy That the absence of ketosis in the fasting adrenalectomized animal does not invalidate this view may be inferred from the finding of Villee and Hastings[110] that acetate the chief immediate precursor of ketone bodies is oxidized to carbon dioxide at a normal rate in the diaphragm of adrenalectomized rats The observations of Thorn et al[101] that a rise in blood ketones and a fall in R Q follow cortisone administration to patients with Addison's disease do not necessarily indicate that this hormone produces an increased oxidation of fat Similar results might be obtained if there were an increased conversion of fat to carbohydrate or a decreased lipogenesis from carbohydrate Evidence for such an effect has been provided by Brady et al[110] who found that cortisone inhibited the incorporation of C^{14} acetate into the fatty acids of rat liver slices

Little is known of the influence of cortisone on phospholipid and cholesterol metabolism Adlersberg et al[131] studying the serum lipids in a variety of conditions observed a gradual increase of total and esterified cholesterol as well as of phospholipid but a sharp decrease of serum neutral fat

MUCOPOLYSACCHARIDES Cortisone has been observed to restore to normal the high serum level of hexosamine in patients with disseminated lupus erythematosus[13] the high blood levels of glucosamine polysaccharides non glucosamine polysaccharides and albumin polysaccharides in patients with rheumatic fever likewise returned to normal[133] The changes observed were associated with clinical remission in both studies Layton[134] has reported that cortisone inhibits the synthesis of chondroitin sulfate a constituent of the connective tissue ground substance by embryonic and healing wound tissue maintained *in vitro* The degree of polymerization of the hyaluronic acid of the joint fluid of patients with rheumatoid arthritis is said to be increased after the intra articular injection of cortisone[135] An inhibitory effect of cortisone upon the activity of hyaluronidase *in vivo* both in animals and in man has been demonstrated[136]

ENZYMES Numerous studies of the influence of cortisone on enzyme systems have been reported [13 135] The major systems on which an action of this hormone has been clearly demonstrated may be summarized as follows Cohen[139] reported that cortisone administration to mice and human beings results in an increase in serum glucuronidase activity Kochakian[140] found that the liver and kidney arginase activity of mice is elevated after the injection of cortisone Umbreit[141] noted that the low activities of liver amino acid oxidase and kidney proline oxidase of adrenalectomized rats could be restored to normal by the administration of the hormone this observation is of some interest in view of the known influence of cortisone on collagen and the fact that of all the proteins of the body collagen is characterized by a high proline content The inhibitory effect of cortisone upon hyaluronidase activity *in vivo* has already been described The increased secretion of pepsinogen that follows cortisone administration in man is discussed below

It is apparent that none of the known effects of cortisone upon enzyme systems gives a clear picture of the mechanisms involved in the over all physiologic actions of the hormone Umbreit[14] points out that in the majority of studies the rates of the various enzymatic reactions tend to be diminished or unchanged after adrenalectomy and to be increased after prior treatment with cortisone It should be particularly emphasized that no effect of cortisone upon enzyme systems has been clearly demonstrated in the absence of the intact cell This fact raises the possibility that the hormone acts by controlling the access of substrate or cofactors to the enzyme within the cell rather than by a direct action on the enzyme it elf

Inorganic Metabolism The effects of cortisone upon electrolyte excretion in man conform in general to the metabolic pattern previously described for DOC and other less highly oxygenated adrenocortical steroids sodium and chloride retention and enhanced potassium excretion [7] However the ultimate effects are considerably more variable and appear to be largely determined by hormone dosage route and duration of administration and in all likelihood by the fundamental state of the adrenal glands in normal persons and the influence of simultaneous DOC therapy in patients with adrenal insufficiency Early studies in normal and adrenalectomized animals utilizing small quantities of cortisone acetate for brief periods conclusively demonstrated that the electrolyte regulating capacity of this hormone was significantly less intense than that of DCA [143 144] Indeed the net result of cortisone administration was in most cases a loss of sodium and chloride It was therefore concluded that one physiologic consequence of 17 hydroxylation of the corticosteroid structure was a marked decrease in the capacity of adrenal steroids to influence the renal handling of electrolytes Although subsequent studies in animals[145] and man[116] showed that more prolonged administration of larger doses of cortisone acetate ordinarily result in sodium retention and potassium elimination the simultaneous administration of DCA and cortisone acetate to patients with Addison s disease has on occasion produced less retention of sodium and chloride than the same quantity of DCA alone [101] In view of the known pharmacologic opposition of these two steroids in their effects upon other functions such as electroshock threshold [146]

it is of interest to consider the possibility of steroidal competition at certain *loci under proper conditions of dosage and functional organization*

ADRENAL INSUFFICIENCY The effects produced upon electrolyte excretion by the administration of cortisone acetate to patients with Addison's disease are variable and unpredictable necessitating careful evaluation in individual cases A relatively small number of patients can be successfully maintained in electrolyte balance on average substitution doses of cortisone acetate (12 5 to 25 mg a day) and supplementary salt Similarly patients with essential hypertension can often be adequately controlled after complete bilateral adrenalectomy by the administration of somewhat larger doses of cortisone acetate (37 5 to 50 mg a day) and additional salt [36] However, the majority of patients with Addison's disease and a significant number *of hypertensive subjects who have undergone total adrenalectomy require* the addition of DCA for the maintenance of adequate electrolyte regulation [47, 113, 147] Comparative studies based on sodium and chloride retention in patients with Addison's disease have indicated that cortisone acetate has approximately one thirtieth to one-fiftieth the potency of DCA [45] Cortisone is somewhat more effective in the control of electrolyte excretion after intramuscular injection than after oral administration reflecting apparently the importance of constant hormonal effect upon the renal tubular mechanisms involved

The effects of maintenance doses of cortisone upon potassium excretion in patients with adrenal insufficiency are highly variable Although an initial slight *increase in urinary potassium output may occur restoration* of balance or even a rebound potassium retention rapidly ensues sometimes a definite decrease in potassium excretion is encountered In such cases it appears that the effects of cortisone upon carbohydrate metabolism are predominant over *renal changes in electrolyte output and that the positive potassium balance* is due to increased storage of liver glycogen This interpretation is strengthened by the observation that inorganic phosphorus output also frequently declines in association with potassium retention [7]

NORMAL SUBJECTS AND PATIENTS WITH INTACT ADRENAL GLANDS *The* administration of large doses of cortisone to both normal subjects and patients with intact adrenal glands is ordinarily followed by definite sodium and chloride retention and an increased excretion of potassium [116, 145] With continued administration of the hormone sodium and chloride retention ordinarily decreases in fact a negative balance may occur as previously described for prolonged courses of DCA An increase in both urinary and fecal excretion of calcium and phosphorus is usually produced by intensive cortisone administration [149] Initially phosphorus output ordinarily exceeds the theoretic excretion of calcium and nitrogen, calculated on the basis of theoretic ratios of calcium to phosphorus and nitrogen to phosphorus in bone and protoplasm, respectively This phenomenon is in all likelihood caused by a significant increase in the renal clearance of phosphorus Subsequently, however, total phosphorus excretion is often less than that anticipated on the basis of theoretic calculations It appears probable that the latter effect is

the result of a movement of phosphate intracellularly in association with an increase in liver glycogen deposition[150] On the basis of actual tissue analyses as well as the calculation of internal balances,[149] it is evident that a significant degree of intracellular potassium and phosphorus depletion may be produced Simultaneously, an intracellular migration of sodium may occur but apparently only in the presence of cellular potassium loss without equivalent phosphorus loss i e relative cation depletion[149] An initial retention of sodium in excess of chloride without a significant change in serum concentration is additional evidence of the movement of sodium into cells

It is apparent on the basis of the over all losses of nitrogen potassium and phosphorus that intracellular protoplasm undergoes depletion as a result of intensive cortisone action This effect alone however, is incapable of accounting for the total pattern of metabolic changes produced For example the loss of potassium precedes that of nitrogen and is in excess of the theoretic protoplasmic nitrogen potassium ratio This is well illustrated in Figure 8 which shows the initial metabolic responses of a normal fasting subject to intravenously infused cortisone The discrepancy between the theoretic nitrogen and potassium contents of protoplasm and the observed excretory pattern is obvious It is of interest to note the rapidity with which maximal changes in electrolyte excretion are produced by the continuous intravenous administration of cortisone In fact the effects obtained are only slightly less intense than those resulting from the intravenous infusion of an equal quantity of DOC This is in direct contrast to the relative potencies of these steroids given by intramuscular injection[7]

Prolonged administration of cortisone in large doses intensifies the effects described above resulting in hypochloremia hypokalemia and metabolic alkalosis The changes are similar to those originally described by Kepler[151] in patients with Cushing s syndrome Simultaneously the electrolyte content of muscle also resembles that encountered in hyperadrenocorticism decreased intracellular potassium and phosphorus with or without increased sodium[15] The administration of testosterone either to patients with Cushing s syndrome or to patients receiving large quantities of cortisone results in a diminution of potassium phosphate and calcium loss[153] Evidence has been presented that the beneficial action of testosterone is the result of a direct anabolic influence on protoplasm rather than a block in the metabolic action of cortisone on end organs[60]

Additional effects on inorganic metabolism resulting from adrenocortical stimulation or the administration of cortisone include a moderate decrease in urinary excretion of magnesium[60] and the production of an acute hypoferremia in dogs[154] the latter effect has not been observed in human subjects

Water Metabolism The first physiologic function of adrenocortical hormones to receive emphasis was the regulation of electrolyte and water metabolism[155] Although it was early recognized that a redistribution of fluid occurred in adrenalectomized animals resulting in a shift of water from the extracellular to the intracellular space[156] most authorities attributed this change to uncontrolled salt loss[157] However numerous studies concerning

the relation of adrenocortical hormones to water metabolism have made it abundantly clear that changes in water distribution cannot be explained solely by an alteration in electrolyte excretion.[155] It is also quite apparent that changes in water excretion after cortisone administration cannot be considered merely a passive response to changing electrolyte levels. For example, cortisone may result in a retention of sodium and water with a consequent expansion of extracellular fluid volume sufficiently great to result in edema. On the other hand, a marked dissociation between the urinary excretion of electrolytes and water sometimes occurs during cortisone administration. Furthermore, since the administration of cortisone in certain circumstances may result in a pronounced water diuresis, it is evident that adrenocortical hormones may exert either a diuretic or an antidiuretic action, depending upon the existing physiologic state of the subject.

ADRENAL INSUFFICIENCY. Striking abnormalities in body water distribution are apparent in patients with adrenocortical insufficiency, consisting of an expansion of intracellular volume at the expense of extracellular volume. It has never been definitely settled whether this redistribution is the result of a change in external sodium balance with a consequent osmotic intracellular shift of water or of an internal movement of salt as well as water from the extracellular fluid space into body cells on the basis of a direct effect at the cellular level. Swingle[159] concluded that an endogenous shift of salt and water from the extracellular compartment into cells in excess of that attributable to hypotonicity secondary to renal salt loss occurred in adrenalectomized dogs. Harrison and Darrow[157] also demonstrated an intracellular movement of water during the development of adrenocortical insufficiency but attributed it entirely to urinary sodium loss. Recent experiments by Gaudino and Levitt[5] appear to confirm the existence of a combined salt and water shift during adrenal insufficiency.

Since the passage of water into red blood cells would result in a dilution of erythrocyte hemoglobin and therefore a fall in the mean corpuscular hemoglobin concentration (M.C.H.C.),[160] changes in this index have been used in this laboratory to study alterations in the distribution of water in patients with Addison's disease during overhydration.[161] During overt adrenal insufficiency an increase in erythrocyte hydration was apparent as evidenced by a fall in M.C.H.C. The intravenous administration of cortisone induced a prompt decrease in erythrocyte volume and a rapid excretion of excess body water. These results are in accord with those of Harrop[156] who showed that adrenocortical extract caused a removal of excess intracellular water, a decrease in mean corpuscular volume and a restoration of normal fluid equilibrium in the adrenalectomized dog.

Rowntree and Snell[16] originally noted, during the course of dilution tests, a decided lag in the onset and extent of water diuresis. The inability to excrete a water load promptly was subsequently made the basis of a useful screening test for adrenal insufficiency.[163] This defect has been the object of numerous studies and has been variously ascribed to delayed absorption of water from the gastrointestinal tract, a decreased glomerular filtration rate

and renal plasma flow abnormally high levels of antidiuretic substances, on the basis of serum[164] and urine[165] assays, either an increased sensitivity to[164] or decreased capacity to inactivate[166] circulating antidiuretic substances, and abnormality of the renal tubules resulting in excessive water reabsorption [158]

Delayed absorption has been ruled out by a lack of diuresis after intravenous injection of fluid[167] and by a normal plasma dilution after water ingestion by patients with Addison s disease [165] Since the administration of DCA to patients with adrenal insufficiency has been shown to restore glomerular filtration rate to normal without materially improving the rate of water diuresis a reduced filtration rate can hardly be implicated Evidence that casts doubt on the importance of circulating antidiuretic substances has been accumulated Hypophysectomized animals[168] and patients with loss of both anterior and posterior pituitary function[169] manifest a defective diuresis although posterior pituitary hormones are presumably absent Recently, patients with Addison s disease were shown to have a normal sensitivity to administered Pitressin that was not altered by cortisone administration [170] Some patients with Addison s disease demonstrate a normal fall in urinary specific gravity after water loading apparently indicating that persistent tubular reabsorption of water is not wholly responsible for the faulty diuresis observed [161] In addition Reforzo Membrives and Repetto[171] found a normal inhibition of tubular reabsorption of water in patients with Addison s disease in response to water loading

The finding of an excessive and prolonged trapping of administered water in the erythrocytes of patients with Addison s disease accompanying a failure of diuresis indicates that defective distribution of a water load may preclude adequate renal excretion [161] Striking improvement in water excretion occurs in these patients during cortisone therapy [47] either with no significant change in the depressed glomerular filtration rate[170] or without a direct correlation between improvement in filtration rate and water diuresis [17] These findings suggest that a normal diuresis is facilitated by an improvement in water distribution as a result of cortisone therapy

Normal Subjects and Patients with Intact Adrenal Glands The administration of cortisone to normal subjects induces an increase in extracellular fluid volume [172] and a decrease in intracellular water content without a marked change in total tissue water [149] Salt and water retention usually occurs early in the course of treatment and reverts to a normal balance in 8 to 10 days [116] The maximal change in body fluid content and distribution ordinarily coincides with a maximal increase in glomerular filtration rate and filtration fraction [173] Cortisone therapy augments the rate of urine flow during constant water loads in subjects with normal adrenal glands without altering the sensitivity to exogenous Pitressin [174] It suppresses the normal diurnal rhythm of water and electrolyte excretion in normal subjects [175]

Further studies on the relation of corticosteroids to the degree of erythrocyte hydration in response to water loading demonstrated an actual contraction of erythrocytes during a water test performed on a patient with Cush

ing's syndrome (Figure 9).[181] After bilateral total adrenalectomy and the onset of clinical remission from this disease, there was a change in the erythrocyte pattern to one much like that seen in Addison's disease. The administration of large doses of cortisone for a three-day period restored the corpuscular pattern to that seen preoperatively, again with contraction of the erythrocytes in response to water. These findings, in the absence of any significant alteration in the magnitude of water retention or in the degree of

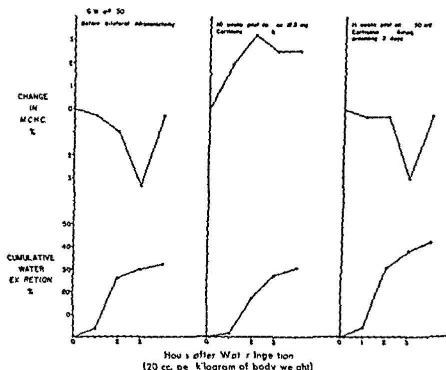


FIG. 9. Water tests in Cushing's syndrome. Cumulative water excretion is expressed as percentage of water ingested. A rise in mean corpuscular hemoglobin concentration (M.C.H.C.) reflects a decrease in erythrocyte size.

hemodilution, suggest that cortisone has an action on the transfer of water into the erythrocytes that is independent of its diuretic effect and that excessive amounts of cortisone-like steroids may induce a paradoxic shrinkage of the erythrocytes despite a normal fall in serum tonicity.

Effects upon Specific Tissues. The characteristic changes in specific tissues of the body resulting from the administration of cortisone are obviously consequent to the widespread metabolic alterations just described. It is to be emphasized therefore that use of the hormone in clinical therapy at high dosage levels entails alterations in the metabolism and potentially in the structure of all tissues. An evaluation of therapy undertaken for the purpose of producing a specific action in a specific tissue or organ system must take into account the over-all effects of the hormone. In short, cortisone

affects such a wide variety of metabolic processes and cellular structures that one must interpret any single hormonal action in terms of the aggregate effects upon the entire organism

Kidney ADRENAL INSUFFICIENCY It has long been recognized that defective renal function constitutes one of the major physiologic disorders of chronic adrenal insufficiency In fact the degree of azotemia resulting from dehydration hemoconcentration reduced plasma volume and diminished renal blood flow has often been used as an index of the severity of adrenal insufficiency in adrenalectomized animals Studies of renal function in patients with Addison s disease have demonstrated a diminished glomerular filtration rate and a less marked decrease in renal plasma flow the filtration fraction is consequently reduced [176 177] These abnormalities are frequently returned virtually to normal by cortisone [177 178] Pitts[10] has postulated on the basis of acute experiments in adrenalectomized animals that the effects of cortisone as well as of DOC do not represent a primary action of these hormones on renal hemodynamics but depend upon the restoration of both volume and composition of body fluids consequent to the reestablishment of electrolyte balance

The capacity of the kidney to compensate for alterations in acid base balance is reduced in adrenal insufficiency This deficit is primarily the result of an impairment of normal base saving mechanisms that depend upon a tubular exchange of hydrogen ions and ammonia for sodium [12] The administration of cortisone has been demonstrated to cause an increased excretion of ammonia and titratable acidity in response to acid loading with a resultant conservation of fixed base It should be pointed out that although the effect of cortisone in the regulation of tubular ion exchange processes and secondarily of renal hemodynamics is similar to that of DOC much larger doses of the former steroid are required [179] This is in keeping with the fact previously emphasized that cortisone is intrinsically much less active than DOC in the control of electrolyte excretion

Although the renal abnormality associated with adrenal insufficiency has not been completely defined there is sufficient evidence that the incapacity to limit salt loss is due to decreased tubular reabsorption of sodium [157 180] However Roemmelt et al [12] have demonstrated that adrenalectomized animals infused with hypertonic saline solution are unable to excrete the administered salt at a normal rate because of increased tubular reabsorption of sodium Similarly Burnett[178] showed that urinary sodium excretion by patients with Addison s disease given 4 per cent sodium chloride solution intravenously was markedly subnormal Neither a significant rise in urine flow nor an increase in urinary sodium concentration was observed The defect was partially corrected by cortisone but little influenced by DOC These studies illustrate an important aspect of cortisone action its effectiveness in increasing renal capacity to change the reabsorptive rate of sodium irrespective of the initial defect probably reflects a fundamental action directed toward the maintenance of homeostasis This concept of adrenal steroid function has been well delineated by Ingle [181]

NORMAL SUBJECTS AND PATIENTS WITH INTACT ADRENAL GLANDS The administration of comparatively large doses of cortisone to normal subjects produces definite alterations in renal function Glomerular filtration rate is significantly elevated renal plasma flow is usually only slightly increased and the calculated or effective flow is ordinarily not significantly changed because of an accompanying fall in venous hematocrit [173,182] Consequently the filtration fraction is increased Since maximal tubular transfer rate of *p* aminohippurate (T_mPAH) was not elevated Burnett et al [178] concluded that cortisone does not produce an increase in kidney mass A rise in glomerular hydrostatic pressure could not be implicated as the cause of increased glomerular filtration rate in normal subjects Although an elevation of blood pressure was observed in patients with Addison's disease the resultant rise in hydrostatic pressure was insufficient to account for the significant changes in filtration rate

Studies carried out by Ingbar et al [182] in normal subjects demonstrated an increased urinary excretion of uric acid and phosphorus after cortisone administration In both instances the rise in urinary output was independent of changes in serum concentration and the ratio of excreted solute to filtered solute rose markedly The changes observed indicate an alteration of tubular transport of uric acid and phosphorus under the influence of cortisone Sodium excretion decreased as a result of increased tubular reabsorption Potassium output however was significantly elevated only during concomitant sodium loading emphasizing again the potential importance of sodium reabsorption as a conditioning factor in the renal excretion of potassium That there is a renal component in the glycosuria that may be induced in man by the administration of cortisone has been indicated by Conn et al [115] who noted glycosuria associated with little or no rise in blood sugar It is evident that a decrease in renal threshold may result from a reduction in maximal tubular transfer rate of glucose (T_m glucose) or an increase in tubular load due to either a rise in blood sugar concentration or an elevation of glomerular filtration rate or a combination of both [183]

Antopol[184] observed granulomatous nodules in the kidneys of mice given relatively large doses of cortisone, and Selye[185] reported that the administration of large doses of this hormone to unilaterally nephrectomized rats receiving a high sodium high protein diet may result in hyalinization of glomerular capillaries and eventually in nephrosclerosis Rich[186] demonstrated, in animals given large doses of cortisone the development of renal lesions that were morphologically similar to the Kimmelstiel-Wilson nodules found in patients with long standing diabetes mellitus Although the majority of clinical reports fail to indicate significant changes in conjunction with cortisone therapy the possibility remains that long continued administration of cortisone at a high dosage level will induce renal changes similar to those reported in cases of spontaneous Cushing's syndrome [187] It is of interest that repeated clinical trials have revealed cortisone to be relatively ineffective in modifying the inflammatory renal lesions of acute glomerulonephritis [188] disseminated lupus erythematosus and polyarteritis although other lesions of

the last two disorders may be remarkably benefited Aggravation of hyper tension and azotemia has been observed with cortisone therapy in patients exhibiting advanced renal disease in association with these syndromes

Effects upon Endocrine System *Anterior Pituitary Body and Adrenal Glands* It is well known that the administration of cortisone to animals and man leads to a suppression of endogenous adrenocortical secretion Several lines of evidence may be cited Patients both male and female with an intact pituitary adrenal system may show a decreased urinary 17 keto steroid output during cortisone therapy (50 to 75 mg a day) After cortisone administration corticotropin may elicit a poor adrenal response as meas

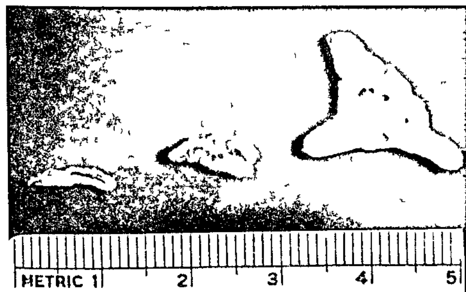


FIG 10 Effect of cortisone upon the adrenal gland The gland on the left was obtained from a four year old girl with acute leukemia who received cortisone 100 mg a day for four weeks before death The gland in the center was from a four year old girl with pulmonary stenosis who died during operation The gland on the right came from a four year old girl with Letterer Siwe disease who received 50 mg of corticotropin daily for three weeks before death (Courtesy Dr Sidney Farber Department of Pathology The Children s Hospital Boston)

ured by eosinophil fall and 17 ketosteroid and formaldehydogenic steroid rise in the urine When cortisone therapy is suddenly withdrawn clinical evidences of adrenal insufficiency such as weakness fatigability hypoten sion and collapse may be observed These signs and symptoms may be accompanied by a relatively high eosinophil count and a low 17 ketosteroid and formaldehydogenic steroid excretion in the urine Indeed death from adrenal insufficiency has been reported under these circumstances [190] Acute adrenal insufficiency is more commonly observed after the withdrawal of orally administered cortisone because of the abrupt decrease in hormonal levels in contrast to the more gradual decline after discontinuation of intra muscularly injected hormone Finally atrophy of the adrenal cortex has

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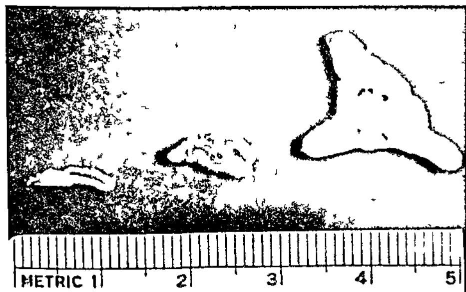


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been repeatedly observed in both animals[191] and man[19] after the administration of cortisone (Figure 10) This atrophy is largely confined to the fascicular and reticular layers, where there is a reduction of lipid concentration The zona glomerulosa remains virtually unchanged

There is strong evidence that the suppression of adrenocortical activity is secondary to the depression of the output of corticotropin by the anterior pituitary body The adrenal response to stress as measured in animal experiments by adrenal hypertrophy and depletion of ascorbic acid and cholesterol *may be blocked by the administration of cortisone With increasing intensity* of stress the amount of steroid required to suppress adrenocortical activity becomes correspondingly greater [193] Furthermore the adrenal atrophy that follows cortisone therapy may be prevented by the simultaneous injection of corticotropin [194] Finally suggestive evidence of a direct effect upon the pituitary gland has been provided by Sayers et al [195] who demonstrated diminished blood levels of corticotropin in patients with adrenogenital syndrome after cortisone therapy The striking similarity of adrenocortical response to corticotropin in patients with hypopituitarism and in patients with intact adrenal glands after a prolonged course of cortisone therapy is illustrated in Figure 11 The possibility remains however that cortisone also exerts a direct effect upon the adrenal gland

Although the suppression of corticotropin output by cortisone seems fairly well established evidence of suppression of the output of other pituitary hormones is not so clear cut It has been suggested that the reduction in the ability of the thyroid gland to collect iodine observed with large doses of cortisone may in part reflect depression of thyrotropic hormone (TSH) liberation [196] However no measurements of TSH blood levels under these conditions have been reported Indeed cytologic studies of the pituitary glands of rats treated with large doses of cortisone for a prolonged period indicate that the beta cells undergo changes comparable to those seen in animals after thyroidectomy a finding suggestive of an increased output of TSH by the pituitary gland [19] Sohval and Soffer[198] have reported an increase in urinary gonadotropin excretion after cortisone administration Information is not available on the possible effects of cortisone upon the secretion of growth hormone and diabetogenic hormone

Posterior Pituitary Body No evidence of a direct action of cortisone on the posterior pituitary gland or on the release of its hormones has been reported The effect of cortisone on the peripheral action of antidiuretic hormone is discussed in the preceding section on Water Metabolism

Intermediary Lobe of the Pituitary Gland The existence of this part of the pituitary gland as a functional unit in man is yet to be established It has been suggested however that the pigmentation of patients with Addison s disease may be related to hyperactivity of the intermediary lobe of the hypophysis[199] and that the lightening of the skin seen with cortisone therapy of hypoadrenalism may result from inhibition of this lobe [200]

Thyroid Gland Clinical data indicate a definite effect of cortisone upon measurements of thyroid function Thus, Wolfson et al [01] and Hill and his

as ociates [92] have demonstrated a decrease in the I^{131} "accumulation gradient" in patients with normal adrenal function or with Addison's disease on moderate doses of cortisone (50 to 100 mg a day). A similar effect with massive doses of cortisone (500 mg a day) on the 24 hour iodine uptake has been demonstrated by Fredrickson et al [196] A decrease in the level of protein-bound iodine during cortisone therapy has also been observed [91 203]

The exact mode of action of cortisone in inhibiting iodine uptake is not clear It appears that this effect is not due to an inhibition of TSH formation or release by the anterior pituitary body [197] Woodbury and his co-workers [94]

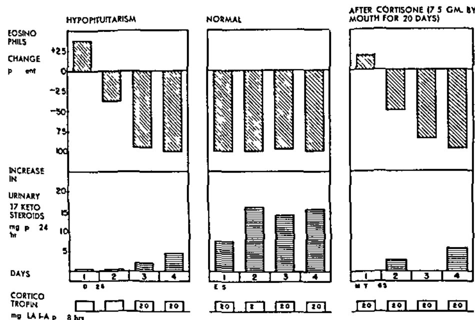


Fig 11 Different adrenocortical responses to daily intravenous infusions of corticotropin All infusions extended over eight hour periods

ob erved in hypophysectomized rats that the increase in I^{131} accumulation that followed the administration of TSH was partially suppressed by cortisone It therefore appears that cortisone exerts its action in part at least by either a direct effect upon circulating TSH or an incomplete block of the mechanism by which TSH influences iodine uptake This view is strengthened by the finding that in hypophysectomized rats cortisone alone does not depress the accumulation of I^{131} by the thyroid gland [94] Perry [95] and Albert et al [96] however have reported that in intact rats the biologic decay of thyroidal radioiodine is not altered by cortisone an indication that the steroid does not interfere with the influence of TSH on this measurement It remains possible that the cortisone effect upon iodine uptake by the thyroid gland reflects alterations in either iodine distribution or excretion [96] It is well to keep in mind that although changes in measurements of thyroid function can be induced by cortisone the relation of these measurements to thyroid hormone production may not be an absolute one The effect of corti

been repeatedly observed in both animals[191] and man[18] after the administration of cortisone (Figure 10). This atrophy is largely confined to the fascicular and reticular layers, where there is a reduction of lipid concentration. The zona glomerulosa remains virtually unchanged.

There is strong evidence that the suppression of adrenocortical activity is secondary to the depression of the output of corticotropin by the anterior pituitary body. The adrenal response to stress, as measured in animal experiments by adrenal hypertrophy and depletion of ascorbic acid and cholesterol, may be blocked by the administration of cortisone. With increasing intensity of stress, the amount of steroid required to suppress adrenocortical activity becomes correspondingly greater.[193] Furthermore, the adrenal atrophy that follows cortisone therapy may be prevented by the simultaneous injection of corticotropin.[194] Finally, suggestive evidence of a direct effect upon the pituitary gland has been provided by Sayers et al.,[195] who demonstrated diminished blood levels of corticotropin in patients with adrenogenital syndrome after cortisone therapy. The striking similarity of adrenocortical response to corticotropin in patients with hypopituitarism and in patients with intact adrenal glands after a prolonged course of cortisone therapy is illustrated in Figure 11. The possibility remains, however, that cortisone also exerts a direct effect upon the adrenal gland.

Although the suppression of corticotropin output by cortisone seems fairly well established, evidence of suppression of the output of other pituitary hormones is not so clear cut. It has been suggested that the reduction in the ability of the thyroid gland to collect iodine observed with large doses of cortisone may in part reflect depression of thyrotropic hormone (TSH) liberation.[196] However, no measurements of TSH blood levels under these conditions have been reported. Indeed, cytologic studies of the pituitary glands of rats treated with large doses of cortisone for a prolonged period indicate that the beta cells undergo changes comparable to those seen in animals after thyroidectomy, a finding suggestive of an increased output of TSH by the pituitary gland.[197] Sohval and Soffer[198] have reported an increase in urinary gonadotropin excretion after cortisone administration. Information is not available on the possible effects of cortisone upon the secretion of growth hormone and diabetogenic hormone.

Posterior Pituitary Body. *No evidence of a direct action of cortisone on* the posterior pituitary gland or on the release of its hormones has been reported. The effect of cortisone on the peripheral action of antidiuretic hormone is discussed in the preceding section on Water Metabolism.

Intermediary Lobe of the Pituitary Gland. The existence of this part of the pituitary gland as a functional unit in man is yet to be established. It has been suggested, however, that the pigmentation of patients with Addison's disease may be related to hyperactivity of the intermediary lobe of the hypophysis[199] and that the lightening of the skin seen with cortisone therapy of hypoadrenalism may result from inhibition of this lobe.[200]

Thyroid Gland. Clinical data indicate a definite effect of cortisone upon measurements of thyroid function. Thus Wolfson et al.[201] and Hill and his

Mitotic figures were rare and new beta cells appeared to arise chiefly by metamorphosis of the exocrine acinar cells in a manner similar to that described by John on [11] in partially depancreatized guinea pig

Becker [15] has drawn an interesting parallel between the diabetes resulting from the administration of cortisone or corticotropin and the type of human diabetes characterized by retinal capillary aneurysms Kimmelstiel Wilson lesions in the kidney and the failure to develop ketosis in the absence of exogenous insulin This author pointed out that persistent ketonemia or acidosis rarely develops in patients with steroid diabetes He reported the appearance of retinal capillary aneurysms in 2 patients who were receiving corticotropin intravenously for sarcoidosis Finally he recalled the observation[15a] that renal lesions of the Kimmelstiel Wilson type may develop in rabbits given cortisone On the basis of these findings it is of interest to speculate that in both steroid diabetes and spontaneous diabetes characterized by capillary aneurysms a relative excess of the hyperglycemic glycogenolytic factor of the alpha cells of the pancreas in the presence of a normal or mildly deficient supply of insulin might explain the defect of hyperglycemia and the capillary damage observed in both retina and kidney [14]

The use of cortisone in the treatment of patients with coexisting Addison s disease and diabetes mellitus provides an illustration of the necessity for evaluating the effects of the hormone upon specific metabolic functions in terms of the benefit to the total organism In spite of an increase in the severity of the diabetic state (reflected in a material rise in insulin requirement) as a result of administration of cortisone in maintenance doses of 12 5 to 25 mg a day the alleviation of the adrenal insufficiency (reflected in increased food intake weight gain and exercise tolerance) produces a marked improvement in the over all physical status of the patient Indeed advantage is deliberately taken of the diabetogenic action of the hormone to protect these patients from the ever present threat of hypoglycemic episodes the net result being a considerable stabilization of the diabetes and a definite facilitation of therapeutic control

Effects upon Integument The administration of cortisone to patients with Addison s disease ordinarily produces striking changes in skin texture and color The skin becomes perceptibly warmer softer and less dry reflecting at least in part an improvement in hydration resulting from the restoration of fluid and electrolyte balance Recent studies carried out in this laboratory employing the Hardy reflectance spectrophotometer have provided objective evidence of the changes that may result from cortisone administration [60] The distinguishing features of the reflectance curves in Addison s disease have been shown to be as follows a significant lowering of the entire curve reflecting the increased deposition of melanin and diffuse pigmentation that is a conspicuous feature of adrenal insufficiency a depression of the curve in the near ultraviolet region indicating the presence of melanoid a degradation product of melanin and a flattening of the curve in the 400 to 470 millimicron area and a loss of the characteristic fluctuations due to oxyhemoglobin a shift that is probably caused by a smaller content of blood

sone upon the over all function of the thyroid gland in terms of hormone output requires further study

The interesting possibility also arises that cortisone aids in the peripheral utilization of thyroid hormone Thus Hill and his associates [92] noted a rise in basal metabolic rate in a hypothyroid patient receiving suboptimal doses of thyroid during cortisone administration Lerman [97] also described a patient with hypothyroidism whose poor response to thyroid was markedly improved by cortisone administration Beierwaltes et al [208] demonstrated a calorigenic effect of cortisone in 2 patients with untreated myxedema It is not clear whether this effect is mediated directly by the steroid or by an increase in thyroid hormone utilization In contrast Wolfson et al [91] speculated that normal thyroid function is necessary for maximum cortisone effect and that a decreased effect of continued cortisone therapy may depend upon secondary depression of thyroid function Evidence for such a supposition is however still tenuous

Gonads There is little information to indicate an effect of cortisone upon gonadal structure and function in man The occurrence of amenorrhea in women and loss of libido in men with Cushing s syndrome suggests a possible gonadal effect of the hormone Menstrual abnormalities are sometimes seen in female patients to whom cortisone is being administered Oligomenorrhea and irregularity of menstrual flow are the usual changes observed Experimental data are conflicting Winter et al [209] showed no significant effect of cortisone upon the prostate and seminal vesicles of rats whereas Antopol[184] noted retarded development of testes seminal vesicles prostate and ovaries of mature mice Brown et al [210] made the interesting observation that corticotropin can inhibit the activity of administered gonadotropin in hypophysectomized rats

Pancreas The effects of cortisone upon carbohydrate metabolism and the relation of this hormone to diabetes mellitus are discussed in the section on Carbohydrate Metabolism

It is important to reemphasize the relatively infrequent occurrence of a significant degree of hyperglycemia and glycosuria in nondiabetic patients receiving cortisone or corticotropin therapy Cases in which these manifestations develop are often those in which a familial tendency to diabetes is evident After withdrawal of the hormones hyperglycemia and glycosuria regularly disappear [11] Even in Cushing s syndrome overt diabetes is comparatively uncommon Although 31 of the 33 patients described by Plotz et al [21] exhibited diabetic glucose tolerance curves only 9 had glycosuria and frank diabetes was present in only 5

Pancreatic lesions in patients with Cushing s syndrome are common The lesions found have included fatty necrosis carcinoma purulent pancreatitis and pancreatic infarcts and cysts in the few cases in which the islands of Langerhans have been carefully studied hyperplasia has been seen [187] The changes produced in the pancreatic islet tissue of rats that had been given large doses of corticotropin have been investigated by Baker [13] Hypertrophy, hyperplasia, and degranulation of the beta cells were observed

lation In view of the decrease in sebum it is of interest that Brunsting [19] has pointed out the fact that acne occurring during the administration of cortisone is not often accompanied by seborrhea

Healing of acute inflammatory lesions of the skin during treatment with cortisone may be accompanied by the local deposition of pigment Local pigmentation is frequently seen in the scar at the site of implantation of cortisone pellets In contrast to the effects of corticotropin however the administration of large quantities of cortisone over prolonged periods does not ordinarily *result in a generalized darkening of the skin*

Effects upon Musculoskeletal System ***Muscle*** Muscle weakness is a cardinal symptom of Addison's disease Furthermore, the capacity of adrenalectomized animals to perform muscular work has served as the basis of tests proposed by Everse and de Fremery [20] and by Ingle[94] for the detection and assay of adrenocortical steroids The latter procedure has proved of inestimable value in the comparative assay of crystalline steroids and in the elucidation of the physiologic actions of these compounds [221] Although the advent of muscular exhaustion in the adrenalectomized animal subjected to continual muscle stimulation is apparently correlated with circulatory failure the probability remains that 11 17 oxysteroids are directly involved in the maintenance of metabolic processes intrinsic to muscle contraction Cortisone has proved considerably more effective than DOC corticosterone and dehydrocorticosterone in the maintenance of muscular capacity in adrenalectomized animals [1] and in patients with Addison s disease It is of interest however that cortisone is definitely less effective in the Ingle work test than aqueous adrenocortical extract On the other hand neither adrenocortical extract nor any crystalline steroids yet available can elevate muscle work output in the adrenalectomized rat to levels characteristic of normal animals *or increase further the work capacity of normal muscle*

During the administration of cortisone to patients without primary muscle disease an increase in creatine excretion is sometimes encountered Preformed creatinine output however remains unchanged In view of the studies of Zierler et al [2 3] on the influence of DCA on the mechanisms of creatine excretion cortisone may also be capable of reducing tubular reabsorption of creatine

Shy et al [4] have shown that the administration of cortisone to patients exhibiting the primary muscular abnormality of myotonia may result in a significant decrease in myotonic response Since the pharmacologic characteristics of myotonia are diametrically opposed to those of myasthenia gravis it is difficult to reconcile this result with the improvement of neuromuscular conduction muscle contractility and strength reported in myasthenia gravis during intensive adrenocortical stimulation [5] It appears that the abnormalities in neuromuscular function in myasthenia gravis are often considerably aggravated during hormone administration with subsequent improvement above control levels of function during the rebound period of relative adrenal insufficiency after hormone withdrawal

During protracted administration of large doses of cortisone muscular

in the reflecting tissues and a relative increase in venous blood content After the institution of maintenance cortisone acetate therapy a generalized and progressive lightening may be demonstrated owing to a decrease in the skin content of melanin The reduction in pigmentation however, is far from complete as indicated by a persistence of the characteristic reflection pattern of melanoid A reversion of the oxyhemoglobin band toward normal undoubtedly reflects improved vascularity and hydration Other changes encountered during substitution therapy with cortisone include an increase in hair growth in the sexual areas and on the extremities At the dosage level ordinarily employed in the treatment of patients with Addison's disease no other changes attributable to androgenic activity have been seen

The employment of large doses of cortisone during prolonged periods of therapy of patients with intact adrenal glands may result in striking changes in the skin comparable to those encountered in patients with Cushing's syndrome A generalized thinning of the skin is sometimes observed and may be accompanied by the formation of violaceous striae The mechanisms of these changes in Cushing's syndrome have been eloquently discussed by Albright [120] who considered the antianabolic effects of adrenal oxysteroids upon protein to be responsible A characteristic rounding of the face is often encountered, constituting an early sign of cortisone overdosage This change in facial appearance is not necessarily correlated with the occurrence of weight gain or edema and has usually been attributed to a local increase in fat deposition The appearance of acne keratosis pilaris and occasionally hirsutism during the prolonged administration of large doses of cortisone reflects the metabolic conversion of this hormone into steroids possessing definite androgenic activity The effects of large doses of cortisone administered both systemically and locally upon the skin of rats have been carefully studied by Baker et al [17] Striking changes in skin structure were produced including a thinning of the epidermis due to an absolute reduction in the number of epithelial cells an almost complete inhibition of hair growth and an atrophy of sebaceous glands The dermis was similarly affected with a pronounced decrease in thickness caused by a melting down of collagen fibers into a compact almost homogeneous mass and an absolute reduction in the number of fibroblasts with shrinkage and pyknotic changes in the nuclei of the cells that survived Elastic fibers were apparently spared It is of interest that inunction of cortisone over a protracted period in these animals had no systemic effects

A careful investigation of the skin in numerous patients representing a large group of dermatoses treated with cortisone and corticotropin has been carried out by Sauer and his associates [218] The results of these studies can be summarized as follows the absorption time of intracutaneously injected saline solution was significantly shortened skin temperature showed a distinct tendency to elevation sweating was augmented sebum and other fat soluble materials delivered at the skin surface were diminished and examination by stereoscopic microscope revealed an enhanced blood flow All the effects listed were interpreted as evidence of an accelerated peripheral circu

A 51 year-old woman with nontropical sprue of 13 years duration and severe generalized osteomalacia sustained bilateral impacted subcapital fractures of the femoral necks as the result of a fall Owing to a complete absence of healing after five weeks of intensive supportive therapy bilateral hip nailing was performed Despite the presence of severe bone disease the oral administration of 100 mg of cortisone acetate a day was begun before operation and continued at this dosage level for one month and at a level of 50 mg a day thereafter For the first time since admission to the hospital diarrhea was controlled and the appetite was markedly improved the patient gained 25 pounds in weight during a three month period Both fractures healed satisfactorily and three months after operation no distinct fracture line was evident

Certainly the over all therapeutic benefits accruing from cortisone therapy in this case overshadowed the risk of interfering with fracture repair, indeed it appears quite probable that the anabolic consequences of increased food intake and improved gastrointestinal absorption resulting from the use of cortisone contributed significantly to a satisfactory process of healing

Joints One of the earliest detectable effects of an elevated adrenocortical secretion in human subjects is the reduction in potential difference between the inner surface of the synovial membrane and a reference electrode applied to the skin In patients with active rheumatoid arthritis the abnormally elevated potential may be reduced by 50 per cent and sometimes to normal values within 20 minutes of effective adrenocortical stimulation [30] A decrease of intra articular temperature in actively inflamed joints has been found to occur within 24 hours of cortisone administration [31] In addition to suppressing inflammatory changes cortisone has been shown to revert the chemical abnormalities of joint fluid to normal After both systemic and intra articular administration of cortisone joint fluid viscosity is elevated reflecting an increase in concentration or polymerization of hyaluronic acid [135] It should be noted however that the beneficial effect of the intra articular injection of hydrocortisone is considerably more consistent than that of cortisone [231]

Effects upon Connective Tissue Numerous observations have been made on the effects of cortisone upon connective tissue and other mesenchymal derivatives [23] Baker [7] has emphasized that all three essential components of connective tissue—cells fibers and ground substances—are susceptible to the actions of the hormone [2, 7] Fibers and ground substances are derived from and dependent upon cells damage to which may have profound effects upon the structure of supporting tissues

Large doses of cortisone delay fibroplasia an action apparently independent of the initiating stimulus Its capacity to inhibit the genesis of fibrils has been demonstrated in cultures of fibroblasts by Sacerdote et al [233] The actions of the hormone on fibroelastic connective tissue have been well demonstrated by Castor and Baker [34] in a study of the effects of prolonged local application to the skin of rats Fibroblasts were materially reduced in number and residual cells were often shrunken Collagenous fibers became arranged in an almost homogeneous compact mass as a result of which the dermis was greatly thinned The ground substance was reduced in amount

function and strength may become seriously impaired It is apparent that the majority of cases result from serious potassium depletion although patients with temporary muscular weakness have been described in whom no significant loss of potassium could be demonstrated [116] Since a decrease in muscle strength is a well recognized component of Cushing's syndrome, a prolonged interference with protein synthesis during chronic cortisone administration may be responsible in part for the impairment of muscle fiber strength

It is of interest therefore that muscular weakness may be a prominent feature of both adrenocortical hormone deficiency and hormone excess It appears that the mechanism most frequently responsible is a significant alteration of serum (and undoubtedly tissue) electrolyte concentrations An extremely useful index for evaluating serum electrolyte content is the readily obtainable ratio of serum sodium to potassium [45] A marked alteration of this ratio in either direction may well result in striking abnormalities in muscular function

Bone and Cartilage The administration of large doses of cortisone ordinarily results in an increased output of calcium and phosphorus Changes in calcium balance are considered to reflect chiefly alterations in bone composition Discrepancies in the anticipated renal excretion of phosphorus based on theoretic ratios of calcium to phosphorus and nitrogen to phosphorus in bone and protoplasm respectively have been attributed to changes in the tubular transfer of phosphorus and to retention in association with increased liver glycogen

Becks et al [2, 6] have shown that intensive adrenocortical hypersecretion results in a derangement of the normal processes of long bone growth in rats as evidenced by a striking reduction in width of the epiphyseal cartilage Baker [7] has also reported decreased proliferation of cartilage cells impairment of resorption and invasion by bone marrow connective tissue and diminished formation of new bone due to a reduction in the number of active osteoblasts Winter and his co-workers [09] described comparable change after prolonged cortisone administration

Osteoporosis may result from long continued administration of cortisone Albright [10] concluded from a classic study of Cushing's syndrome that an antianabolic action of oxysteroids of the cortisone type could account for osteoporosis A decrease in the formation of osteoid matrix resulting from the interference with protein synthesis is probably responsible for calcium and phosphorus loss A direct effect upon calcium excretion may accentuate the loss due to diminished calcium deposition Reports of pathologic fractures in patients treated for long periods with cortisone [9, 9] serve to emphasize the potent effect of the hormone upon bone formation

Although the direct effects of cortisone upon bone structure are recognized as being antianabolic the following case emphasizes the importance in clinical therapy of evaluating the net effects of the hormone upon a specific tissue in terms of the over all effects of the hormone upon the total organism

sone upon wound healing It was decisively demonstrated that protein depletion produced by starvation facilitated the interference with wound healing by cortisone and conversely that the administration of cortisone accentuated impairment of healing due to protein depletion It is apparent that marked differences in the effects of adrenal steroids upon wound repair in debilitated and in adequately nourished patients should be taken into consideration

Cortisone has been demonstrated to exert an inhibitory effect upon the development of pericardial pleural [43] and peritoneal[244] adhesions experimentally produced in animals with talc A practical extension of this effect appears to be the increase in mobility produced by cortisone in patients with Dupuytren s contracture [245] It is of interest that growth hormone in contrast to cortisone and corticotropin enhances the granulomatous response to injurious substances [246] This observation appears to support the hypothesis that growth hormone and adrenocortical steroids are antagonists in their action on the inflammatory potential of connective tissue

Although the predominant influence of high doses of cortisone on protein metabolism is an interference with protein synthesis it should be pointed out that this action can often be modified or even reversed during therapy as a result of the salutary effect of the hormone upon appetite and improvement of protein and caloric intake The most striking illustration of this phenomenon of cour e is found in patients with Addison s disease after institution of cortisone therapy A markedly improved sense of well being and stimulation of appetite ordinarily result in a significant often pronounced weight gain It is obvious that the increase in protein intake so far outweighs the potential deleterious effects upon protein metabolism of the small substitution doses employed that the net effect of the hormone is a stimulation of tissue anabolism Similarly in certain carefully selected patients with chronic inflammatory disease a judicious regulation of cortisone dosage may permit a sufficient stimulation of caloric and protein intake to offset materially although indirectly any impairment of protein formation The final effect of cortisone upon protein metabolism and other primary actions of the hormone must therefore be evaluated in terms of the entire range of metabolic changes elicited

Effects upon Hemopoietic System Characteristic changes in the pattern of circulating blood cells are encountered in states of hypoadrenalism and adrenal hyperfunction In addition to hemoconcentration the blood of the majority of patients with Addison s disease exhibits the following abnormalities a normochromic normocytic anemia and a subnormal white cell count with an increase in the number of lymphocytes and normal to high levels of eosinophils Although DOC therapy will lead to an increase in plasma volume with alleviation of the hemoconcentration only cortisone will cause the cellular changes to revert to normal [48] In Cushing s syndrome eosinopenia is observed in a high percentage of cases lymphopenia is encountered less frequently whereas polycythemia is found in approximately half the cases

The marked effects of corticotropin upon lymphocytes[247] and circulating

and evidence of actual chemical alteration was obtained Elastic fibers were apparently unaffected and therefore appeared more concentrated In addition all epithelial structures, including hair and sebaceous glands underwent regression and subcutaneous fat almost completely disappeared

Lymphoid organs are essentially composed of parenchymal cells embedded in a network of reticular connective tissue The significance of the reticulum has been well stated as follows by Baker [13]

> In a sense the reticular connective tissue cell represents the retention in the adult body of a primitive form which possesses many potentialities for development It may give rise to any of the various types of blood cells phagocytes and other cells Therefore what happens to it in the hyperadrenal state is of utmost importance to the well being of the body

Intensive cortisone administration has been demonstrated to produce extensive disintegration of the reticular network, with shrunken cells containing irregular and frequently pyknotic nuclei and fragmented reticular fibers Furthermore evidence of an inhibition of lymphocyte and thymocyte production has been derived from the scarcity of cells that are transitional between reticular connective tissue cells and more mature forms and from actual degeneration of the progenitor reticular cells themselves [235] Evidence concerning the effects of adrenal hormones upon the phagocytic activity of the reticulo-endothelial system is conflicting Gordon and Katsh[236] described an acceleration of splenic phagocytosis Spain et al [237] however noted a diminished phagocytic response in cortisone treated animals It appears possible from the extensive structural changes described above that prolonged and intensive hormone administration may well interfere with the phagocytic capacity of the reticulo-endothelial system

It appears well established by numerous studies in both animals [38, 39] and man[240] that the administration of large quantities of cortisone may delay wound healing Delayed wound healing has also been frequently observed in patients with Cushing s syndrome It is of particular interest that local application of cortisone to wounds effectively inhibits granulation providing evidence for a direct action on processes of growth [241]

The retardation of wound healing by cortisone has been shown to involve a depressant action on many phases of the healing process including fibroplasia, vascularization and the deposition of extracellular ground substance Although the inflammatory elements are largely suppressed only a slight interference with epithelization has been observed Changes described in the course of experimentally produced wounds in animals receiving large doses of cortisone have included a delay in the appearance of edema after wounding a thinning of the surface layer of red blood cells and fibrin and a paucity of white blood cells a significant delay in the onset of fibroplasia and an abnormal appearance of the fibril bundles a delay in onset of vascularization and an abnormal degree of capillary dilatation, and an over all thinning of adjacent tissues

Findlay and Howes[242] carried out an investigation of fundamental importance on the relation of protein nutrition and depletion to the effect of corti

demonstrated by Hills et al [45] and many others This effect is transient, and with continuing administration of the hormone a gradual return to normal lymphocyte levels in the peripheral blood usually occurs Like the eosinopenia following cortisone the lymphopenia can be prevented by heparin *in vivo* [257] One of the factors in cortisone induced lymphopenia may be an accumulation of lymphocytes in the bone marrow as shown by Yoffey and his coworkers [58] An *in vitro* destruction of these cells in the presence of adrenocortical extract has however been demonstrated by Feldman [59] Heilman [60] likewise showed a necrotizing effect of cortisone upon lymphocytes in tissue cultures Baldridge and his associates [61] however were unable to demonstrate cytotoxic effects of this hormone upon human lymphocytes in cultures of the buffy coat

The lymphopenic effect of cortisone is not confined to the peripheral blood Fixed lymphoid tissue such as the thymus and lymph glands [47] and temporarily at least the abnormal cells of lymphosarcoma and chronic lymphatic leukemia [148] are sensitive to the action of the hormone

Neutrophils It has been clearly demonstrated that cortisone will often produce a striking neutrophilia [116] [6] This effect appears to be due to stimulation of the bone marrow Indeed myeloid hyperplasia has been observed after cortisone administration to animals [63]

Erythrocytes Cortisone has been shown to cause a significant reticulocytosis and an improvement of anemia in a variety of conditions such as rheumatoid arthritis and Still s disease [26] and disseminated lupus erythematosus Since little or no improvement of anemia has been observed when the clinical response has been poor it is believed that the cortisone effect in these patients is dependent more upon the control of the underlying disease than upon a specific stimulation of the bone marrow A reticulocytosis has been observed to follow the administration of cortisone to patients with pernicious anemia [64] No reports of the occurrence of polycythemia in association with cortisone treatment have appeared

Platelets No effect of cortisone upon the number of platelets or megakaryocytes has been observed in man in conditions in which there is no abnormality of these elements [6] The hormones are ineffective in thrombocytopenic purpura when the marrow is hypoplastic or when platelet formation has been depressed by chemical intoxication or irradiation In states in which the thrombocytopenia is associated with normal bone marrow, particularly in idiopathic thrombocytopenic purpura, however the administration of cortisone may cause the number of platelets in the peripheral blood to return to normal [26] It is of interest that in these conditions the bleeding time may become normal before any change in platelet counts is observed Similarly cortisone may control the hemorrhagic manifestations of aplastic anemia disseminated lupus erythematosus and leukemia although platelet counts may not change [66]

Blood Coagulation There is a variance of opinion about the effect of cortisone upon blood coagulation Prompted by the observation that cortisone and corticotropin therapy was attended by an increased incidence of

eosinophils [48, 249] have stimulated numerous investigations of the action of cortisone on the hemopoietic system

Eosinophils A fall in the peripheral eosinophil count is now recognized as the most striking effect of cortisone upon cellular constituents of the blood The magnitude of this fall varies with the dosage and route of administration of the hormone [50, 51] and is probably proportional to the concentration of steroid attained in the blood stream Studies indicate that the eosinopenic action of cortisone is as rapid and effective when the hormone is administered by the oral route as when it is given intravenously Because of slow absorption of intramuscularly injected cortisone on the other hand far larger doses have to be given by this route to produce an equivalent action [118, 50] Eosinopenia may persist for a prolonged period in the presence of a high blood level of steroid

Three main explanations are offered for the eosinopenic action of cortisone The first attributes the effect to an inhibition of the production or release of eosinophils in the bone marrow The second proposes that eosinophils are caused to enter and to be segregated in such organs as the spleen and the lungs The third theory postulates that cortisone exerts a destructive influence on the eosinophils Evidence that a bone marrow effect may be a factor in the eosinopenia has been provided by Rosenthal et al [5] who during *cortisone treatment of 7 patients with nonhematologic disease* observed decreases in the blood eosinophil counts in all cases (64 to 100 per cent) and consistent increases in the bone-marrow eosinophil count (42 to 372 per cent) Gordon and his associates[252] have noted however that large doses of cortisone result in a marked decrease in the eosinophil content of bone marrow in mice That sequestration of eosinophils may occur under the influence of cortisone has been suggested by demonstration of a significant drop in the number of the circulating eosinophils during passage through the lung [54] No conclusive evidence for the participation of such a mechanism in the eosinopenia resulting from adrenal activation or cortisone administration has yet been presented It has been adequately demonstrated that splenectomy in man does not alter the capacity of adrenal steroids to induce *eosinopenia* [248] Padawer and Gordon[255] have presented strong evidence in support of the view that cortisone has a destructive effect upon the eosinophil, they have observed progressive degenerative changes in the eosinophils in the blood and the peritoneal and pleural fluids of rats after administration of this hormone Furthermore Muehrcke et al [56] have demonstrated *in vitro* a fall in the eosinophil count of blood incubated for four hours in constant contact with cortisone acetate although in very high concentration (1 mg per 3 cc of blood) This evidence is the more convincing since it has been shown that heparin would block this effect *in vitro*[256] as it does also *in vivo* [57] However the significance of these studies in relation to the actual process of eosinopenia *in vivo remains to be demonstrated*

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eosinophils [48, 49] have stimulated numerous investigations of the action of cortisone on the hemopoietic system

Eosinophils A fall in the peripheral eosinophil count is now recognized as the most striking effect of cortisone upon cellular constituents of the blood The magnitude of this fall varies with the dosage and route of administration of the hormone[250, 51] and is probably proportional to the concentration of steroid attained in the blood stream Studies indicate that the eosinopenic action of cortisone is as rapid and effective when the hormone is administered by the oral route as when it is given intravenously Because of slow absorption of intramuscularly injected cortisone on the other hand far larger doses have to be given by this route to produce an equivalent action [116, 50] Eosinopenia may persist for a prolonged period in the presence of a high blood level of steroid

Three main explanations are offered for the eosinopenic action of cortisone The first attributes the effect to an inhibition of the production or release of eosinophils in the bone marrow The second proposes that eosinophils are caused to enter and to be segregated in such organs as the spleen and the lungs The third theory postulates that cortisone exerts a destructive influence on the eosinophils Evidence that a bone marrow effect may be a factor in the eosinopenia has been provided by Rosenthal et al [52] who during cortisone treatment of 7 patients with nonhematologic diseases observed decreases in the blood eosinophil counts in all cases (64 to 100 per cent) and consistent increases in the bone marrow eosinophil count (42 to 372 per cent) *Gordon and his associates* [53] *have noted however that large doses of* cortisone result in a marked decrease in the eosinophil content of bone marrow in mice That sequestration of eosinophils may occur under the influence of cortisone has been suggested by demonstration of a significant drop in the number of the circulating eosinophils during passage through the lung [54] No conclusive evidence for the participation of such a mechanism in the eosinopenia resulting from adrenal activation or cortisone administration has yet been presented It has been adequately demonstrated that splenectomy in man does not alter the capacity of adrenal steroids to induce eosinopenia [48] Padawer and Gordon[255] have presented strong evidence in support of the view that cortisone has a destructive effect upon the eosinophil they have observed progressive degenerative changes in the eosinophils in the blood and the peritoneal and pleural fluids of rats after administration of this hormone Furthermore Muehrcke et al [56] have demonstrated *in vitro* a fall in the eosinophil count of blood incubated for four hours in constant contact with cortisone acetate although in very high concentration (1 mg per 3 cc of blood) This evidence is the more convincing since it has been shown that heparin would block this effect *in vitro* [56] as it does also *in vivo* [57] However the significance of these studies in relation to the actual process of eosinopenia *in vivo* remains to be demonstrated

Lymphocytes The work of Dougherty and White [47] showed a fall in the number of circulating lymphocytes after injection of cortisone and corticotropin in rats mice and rabbits A lymphopenic action in man has been

demonstrated by Hills et al [49] and many others This effect is transient, and with continuing administration of the hormone a gradual return to normal lymphocyte levels in the peripheral blood usually occurs Like the eosinopenia following cortisone the lymphopenia can be prevented by heparin *in vivo* [257] One of the factors in cortisone induced lymphopenia may be an accumulation of lymphocytes in the bone marrow as shown by Yoffey and his co-workers [58] An *in vitro* destruction of these cells in the presence of adrenocortical extract has however been demonstrated by Feldman [259] Heilman [60] likewise showed a necrotizing effect of cortisone upon lymphocytes in tissue cultures Baldridge and his associates [61] however were unable to demonstrate cytotoxic effects of this hormone upon human lymphocytes in cultures of the buffy coat

The lymphopenic effect of cortisone is not confined to the peripheral blood Fixed lymphoid tissue such as the thymus and lymph glands [47] and temporarily at least the abnormal cells of lymphosarcoma and chronic lymphatic leukemia [145] are sensitive to the action of the hormone

Neutrophils It has been clearly demonstrated that cortisone will often produce a striking neutrophilia [116] [6] This effect appears to be due to stimulation of the bone marrow Indeed myeloid hyperplasia has been observed after cortisone administration to animals [63]

Erythrocytes Cortisone has been shown to cause a significant reticulocytosis and an improvement of anemia in a variety of conditions such as rheumatoid arthritis and Still s disease [26] and disseminated lupus erythematosus Since little or no improvement of anemia has been observed when the clinical response has been poor it is believed that the cortisone effect in these patients is dependent more upon the control of the underlying disease than upon a specific stimulation of the bone marrow A reticulocytosis has been observed to follow the administration of cortisone to patients with pernicious anemia [64] No reports of the occurrence of polycythemia in association with cortisone treatment have appeared

Platelets No effect of cortisone upon the number of platelets or megakaryocytes has been observed in man in conditions in which there is no abnormality of these elements [6] The hormones are ineffective in thrombocytopenic purpura when the marrow is hypoplastic or when platelet formation has been depressed by chemical intoxication or irradiation In states in which the thrombocytopenia is associated with normal bone marrow particularly in idiopathic thrombocytopenic purpura however the administration of cortisone may cause the number of platelets in the peripheral blood to return to normal [26] It is of interest that in these conditions the bleeding time may become normal before any change in platelet counts is observed Similarly cortisone may control the hemorrhagic manifestations of aplastic anemia disseminated lupus erythematosus and leukemia although platelet counts may not change [266]

Blood Coagulation There is a variance of opinion about the effect of cortisone upon blood coagulation Prompted by the observation that cortisone and corticotropin therapy was attended by an increased incidence of

thromboembolic complications Cosgriff, Diefenbach, and Vogt[247] investigated the effects of these drugs upon blood coagulation. They found that cortisone 100 mg daily induced a great decrease in clotting time in all 5 patients investigated with no effect upon the heparin retarded clotting time, the prothrombin time or the circulating heparin like substances. Similar findings were obtained by Codlowski.[257] Monto et al[68] on the other hand reported that cortisone and corticotropin produced a transient initial increase in clotting time and in circulating heparin like substances followed after 24 hours by a decreased clotting time in 12 out of 20 patients. Fahey[69] however observed no blood coagulation changes in patients given large doses of cortisone by both oral and intramuscular routes.

Effects upon Cardiovascular System *Blood Pressure* The occurrence of hypotension in patients with adrenocortical hypofunction and a high incidence of hypertension in adrenocortical hyperfunction is well known and has long stimulated speculation concerning a possible supportive role of the adrenal cortex in essential hypertension.[70] The observation that the development of Addison's disease in a patient with essential hypertension is ordinarily followed by a return of blood pressure to normotensive or even hypotensive levels directly suggests a failure of mechanisms involved in the maintenance of the hypertensive state after the loss of adrenocortical function. Recent studies of the effects of total[36] and subtotal[271] adrenalectomy in patients with hypertension are indicative of the intense interest that surrounds the important question of a possible relation between the adrenal cortex and the hypertensive state.

Numerous studies have been carried out concerning the effect of adrenalectomy in experimental hypertension[7 73] and the relation of DOC to both functional[2 4] and structural[275] alterations in the cardiovascular system. Comparatively few reports are available, however, on the influence of cortisone on circulation. The administration of the hormone to unilaterally nephrectomized rats maintained on a high sodium high protein intake has resulted in hypertension.[18] After adrenalectomy renal hypertension in the rat has been restored by the administration of cortisone.[76] In addition hypertensive effects of cortisone have been demonstrated in nephritic (cytotoxic serum) rats before and after adrenalectomy.[277] Although cortisone has been shown to cause a resolution of the inflammatory component of DOC induced hypertensive arteritis in rats, no influence on nephrosclerosis was evident and the onset of hypertension was somewhat accelerated.[278] It therefore appears that the capacity of cortisone to increase arterial pressure is like that of DOC accentuated in the presence of renal damage and states of adrenal insufficiency.[2 9] The administration of cortisone to dogs has been shown to produce a definite rise in plasma hypertensinogen levels unaccompanied by a rise in blood pressure.[80] No effect upon hypertensinogen levels in human subjects could be demonstrated. The observations of Rich[136] on the development in rabbits of vascular lesions strikingly similar to nodules of the Kimmelstiel Wilson type are described above.

The administration of cortisone alone has been demonstrated to be

capable of correcting peripheral vascular failure encountered in acute adrenocortical insufficiency For maintenance therapy on the other hand, the majority of patients with Addison's disease require small doses of DOC in addition to daily substitution doses of cortisone Growing experience with the use of cortisone therapeutically has made it evident that the administration of moderate doses (50 to 150 mg daily) to normal persons rarely produces a significant rise in blood pressure Even doses as large as 300 to 500 mg given daily by intramuscular injection or by mouth over prolonged periods have been found to cause only a slight rise in blood pressure in occasional patients These findings are in agreement with those of Sprague et al [116] who observed an elevation in blood pressure in only 1 of 33 patients on long continued cortisone or corticotropin therapy Perera[281] has emphasized the occurrence of hypertension during cortisone therapy in patients with impaired renal function an experience that coincides with the results achieved by administration of the hormone to animals with acute renal damage [28]

It has been observed that under certain circumstances cortisone may actually reduce blood pressure This action has occasionally although not consistently been seen after administration to patients with essential hypertension [32,283] Similarly both hypotensive [34] and hypertensive [78] effects of cortisone have been reported in rats made hypertensive by the administration of DCA That cortisone is able to counteract an elevation of blood pressure due to certain abnormal patterns of adrenocortical steroid secretion has been convincingly demonstrated by Wilkins et al [285] who recorded the restoration of normal blood pressures in 3 hypertensive patients with congenital adrenal hyperplasia after treatment with cortisone acetate

Peripheral Circulation An increase in capillary resistance in human subjects treated with cortisone has been reported by Robson and Duthie [286] Confirmatory evidence has been obtained by the intravenous infusion of T 1824 dye in wounded cortisone treated animals [24] The diffusion of dye into the wounds of these animals was demonstrated to be less than that occurring in the wounds of control animals not receiving cortisone It is of interest that Swingle[67] arrived at a similar conclusion many years ago concerning the relation of adrenal hormones to capillary permeability on the basis of infusion experiments in adrenalectomized dogs

Recently Ramey et al [57] showed that infusion of norepinephrine produced a rise in blood pressure that was smaller in adrenalectomized than in normal dogs and that the administration of adrenocortical extract (but not DOC) caused a significant rise in blood pressure in adrenalectomized animals receiving simultaneous intravenous infusions of norepinephrine Further work by Fritz and Levine [88] demonstrated that the responsiveness of the vessels of the rat s mesoappendix to the topical application of norepinephrine was reduced by adrenalectomy and subsequently restored by the local application of aqueous adrenocortical extract Again DOC proved inactive Similarly human subjects respond to norepinephrine and Neo-Synephrine with a brisk rise in blood pressure after complete bilateral adrenalectomy during the administration of adequate doses of cortisone acetate

The observations of Brust, Ransohoff, and Reiser [89] are of interest in relation to the possible effects of cortisone and corticotropin upon humoral mechanisms affecting vascular tone. The administration of cortisone to both normotensive and hypertensive subjects resulted in a significant decrease in the hypotensive response to tetraethylammonium chloride (TEAC). With continued administration of the hormones the normal depressor effects of TEAC were eventually converted into a pressor rise. DOC proved ineffective. The responses were independent of sodium retention and often preceded the maximal eosinopenic response to the hormones. These studies were considered to demonstrate that certain vascular effects of cortisone and corticotropin may be mediated by an unidentified humoral mechanism that is potentiated by autonomic blockade.

The increased cutaneous blood flow and the changes in renal hemodynamics that may result from the administration of cortisone have already been described. Myers and Taylor [90] have demonstrated a significant rise in hepatic blood flow and an increase in splanchnic oxygen consumption.

The marked vascular fragility of patients with Cushing's syndrome is well known. Similar changes may be seen after the protracted administration of large quantities of cortisone. It has been suggested[120] that this alteration of vascular structure represents an additional example of the fundamental action of the hormone on protein formation.

Since cortisone may increase plasma cholesterol levels, studies of its effect on atherogenesis have been carried out. Stamler et al. [291] found a significantly greater incidence and severity of aortic and coronary atherosclerosis in cortisone-treated chicks receiving a high cholesterol diet. Etheridge and Hoch-Ligeti [?] described an increased deposition of lipid in the intima and media of patients under 11 years of age after prolonged therapy with cortisone or corticotropin. Because of the apparent correlation between the serum level of giant cholesterol-containing lipoproteins of the S_f 10-20 class with atherosclerosis in human beings, Bloom and Pierce [93] studied the effect of cortisone upon these substances. After administration of the hormone for periods as long as 19 months, however, no definite alteration in lipoprotein level could be demonstrated. It is of interest that a comparable study in rabbits revealed pronounced changes in lipoprotein pattern indicating that cortisone induced a "metabolic block" at the level of S_f 40-80 class of lipoproteins with a resultant accumulation of higher S_f molecules [94].

Cardiac Function. Few studies have been reported on the action of adrenocortical steroids on cardiac function. Perera [81] reported a slight decrease in cardiac output after cortisone in 1 hypertensive subject. Horwitz and his associates[295] also noted a mild decrease in cardiac output in normotensive patients with rheumatoid arthritis during cortisone therapy but considered the effect largely secondary to a fall in cardiac rate as a result of the improvement in inflammatory disease. Patients with Addison's disease often show various nonspecific abnormalities of the electrocardiogram (ECG). These nonspecific abnormalities may be manifested as T waves that are flat or inverted, a prolongation of the Q-T, P-R, or Q-S interval, low voltage

and depression of the S-T segment Somerville et al [96] demonstrated that the administration of cortisone in maintenance doses frequently results in a significant improvement or even complete reversion, of these cardiographic abnormalities Comparative studies of the ECG in patients with Addison's disease and Cushing s syndrome [97] described the interesting finding that the P R interval tends to be in the upper range of normal or abnormally long in adrenal insufficiency whereas the opposite situation obtains in hypercorticism The mechanisms by which cortisone influences the electric activity of the heart remain unknown

Effects upon Gastrointestinal System Cortisone has been shown to have the same qualitative effects as DOC upon the electrolyte content of saliva It causes a reduction in the sodium and an increase in the potassium concentration with a resulting fall in the ratio of sodium to potassium [0] similar to that described under 11 Desoxycortisone

The influence of the adrenal cortex on gastric secretion has received considerable study Tuerkischer and Wertheimer [98] first demonstrated in rats that adrenalectomy produced an increase in the pH and mucin content of fasting gastric juice and a reduction in the volume acidity pepsin and renin content of the secretion stimulated by cholinergic drugs These changes could all be reversed by the administration of adrenocortical extracts Numerous studies by Gray and his associates [99–301] established the clinical importance of the effects of adrenal steroids upon gastric function Cortisone has been shown both in normal persons and in patients with Addison s disease to cause an increase in the basal and nocturnal hydrochloric acid secretion associated with a pronounced rise in the pepsin content of gastric juice This elevation in peptic activity was reflected in a greatly increased urinary excretion of uropepsin the output of which was frequently raised to the high levels encountered in patients with peptic ulceration No effect upon urinary uropepsin occurred in patients with pernicious anemia (atrophic gastritis) or in patients previously subjected to total gastrectomy Experimental observations demonstrated that the action of oxysteroids in augmenting the volume and acidity of gastric juice occurs in dogs with denervated as well as innervated gastric pouches [30] In man the administration of cortisone to patients who have undergone vagotomy has been found to produce an increase in uropepsin excretion [303] It thus appears that the action of cortisone on the cells of the gastric mucosa may be a direct one and not mediated through nervous pathways It has not been possible however to demonstrate such an effect *in vitro* [304]

The development of gastric or duodenal ulcers or the aggravation of persisting ulcers in patients under treatment with cortisone or corticotropin has been reported by Gray et al [301] Kirsner Klotz and Palmer [305] and others It has been suggested from these results that psychogenic and other stress factors long considered of etiologic importance in patients with peptic ulcer may bring about their adverse effects through the influence of an elevated level of circulating adrenal steroids on gastric secretion Observations in this laboratory have confirmed the high degree of sensitivity of a rise in urinary

uropepsin excretion as an index of adrenocortical stimulation In fact, a high correlation exists between the urinary content of uropepsin and 17 hydroxy corticosteroids after adrenocortical activation

A consistent, though slight, fall in serum bilirubin levels has been repeatedly observed with the administration of cortisone and corticotropin to patients with chronic liver disease [306,307] Flink and Williams[308] have described a decrease in serum bile acid levels after the administration of corticotropin to patients with biliary cirrhosis Although these effects have been ascribed to an anti inflammatory action of the oxysteroids recent studies in this laboratory [309] have indicated that increased biliary excretion may play a role Bile was obtained by duodenal intubation before and after cortisone administration to a series of normal persons and to patients with hepatic and pancreatic disorders After the intravenous injection of 50 to 100 mg of cortisone acetate, an increase in the rate of bile flow and in the concentration of bilirubin in the duodenal fluid was consistently observed

No studies of the influence of cortisone on intestinal absorption in normal subjects or patients with Addison's disease have been reported The promotion by this hormone of fat protein and vitamin A absorption in patients with nontropical sprue, however, has repeatedly been observed [310] The mechanism of this effect is unknown

Effects upon Nervous System In 1944 Heinbecker[311] reported 4 cases of Cushing's syndrome in which degenerative changes in the cells of the paraventricular nuclei could be demonstrated It was suggested that these changes could be indicative of a hypothalamic disorder responsible for the well recognized abnormality of pituitary adrenal function in this disorder The subsequent report of Castor et al [312] however indicated that these lesions were in all probability the result of hyperadrenocortical activity rather than the cause of the disease These workers observed that in cortisone treated rats chromatolysis and cytoplasmic vacuolation developed in *the hypothalamic paraventricular and supraoptic nuclei as well as in many* nuclei of the thalamus

The EEG which in cases of Addison's disease is characteristically slow and not materially benefited by salt or DOC therapy reverts to normal in a high percentage of patients receiving maintenance doses 25 mg a day, of cortisone acetate [313] Abnormal EEG's have frequently been encountered in patients with Cushing's syndrome[314] or after the administration of cortisone or corticotropin [315,316] These changes do not appear to be related to alterations in carbohydrate metabolism Lidz and his co-workers[316] found no correlation between alterations in the EEG and changes in mood and behavior observed in patients who demonstrated mental disturbances while receiving cortisone Convulsive seizures have been reported with sufficient frequency during intensive cortisone therapy to indicate a significant effect of adrenocortical hormones upon brain excitability [31] It appears however that in most cases the precipitation of convulsions by cortisone has occurred during the treatment of diseases known to involve the central nervous system These observations are of interest in view of Woodbury's[146] demonstration

that cortisone is capable of increasing the excitability of the brain as indicated by a lowering of the electroshock seizure threshold

It has been suggested that the beneficial effects of cortisone and corticotropin upon diseases such as rheumatoid arthritis are in part due to an analgesic action of these hormones Crokoest et al [318] evaluated cutaneous dental and visceral pain in patients with rheumatoid arthritis before and during the administration of cortisone and corticotropin Cutaneous pain was tested by intradermal injections of saline solution and distilled water tooth sensitivity by electric stimulation and visceral pain by distention of a balloon placed in the duodenum The pain threshold and intensity were similar before and during the administration of the hormones and no true analgesia could be detected

Mental symptoms may be prominent in patients with untreated Addison s disease or may be so mild as to escape casual observation Inability to concentrate and periods of drowsiness may alternate with restlessness and insomnia As the disease progresses patients become increasingly irritable and apprehensive Although these symptoms may diminish with DOC therapy still greater improvement in the patient s mental state occurs when cortisone is given along with DOC

The patient with Cushing s syndrome may likewise show mental disturbances In a recent review Plotz Knowlton and Ragan[314] report that mental symptoms ranging in severity from irritability and depression to major psychoses occurred in one third to two-thirds of patients with Cushing s syndrome The mental illnesses included hysteria suicidal depression states simple schizophrenia and paranoia Of particular interest to the clinician are the psychologic changes that may occur in patients receiving cortisone therapy [319] Paresthesias in the frontal portions of the head usually described as a sense of heaviness fullness or fuzziness are commonly noted There is often an increase in appetite Loss or increase of libido may be seen Euphoria which is an early and frequent symptom is not necessarily related to the relief of pain or disability since it may be seen in the normal subject given cortisone Brody[320] has reported a series of patients in whom the euphoria was soon replaced by psychotic reactions such as delusions depressions hostility and ambivalence which could be correlated with former behavior patterns and seemed to be exacerbations of them He considered that the rapid action of cortisone in alleviating physical symptoms was experienced by these patients as a threat to the neurotic equilibrium

In other patients receiving cortisone therapy thinking and behavior may be accelerated to the point of mental excitement restlessness wakefulness and a rapidly fluctuating mood A detailed description of the more severe mental disturbances that may complicate treatment with cortisone or corticotropin is contained in Chapter 15

Effects upon Growth An impressive array of evidence demonstrates that under certain conditions body growth is suppressed by oxycorticosteroids[145] or by intensive adrenocortical stimulation with corticotropin [3 1] Cortisone fails to sustain normal growth rate in young immature adrenalectomized

rats[322] and in large doses frankly inhibits growth in mature adrenalectomized[323] and normal[209] rats. Furthermore, inhibition may be extreme, despite a greatly increased food intake during cortisone administration. Since high level cortisone treatment may interfere with growth of epiphyseal cartilage in immature animals and suppress chondrogenesis and osteogenesis in mature rats,[7] it is not surprising that elevated levels of corticosteroids antagonize the somatotrophic effects of growth hormone.[26] Other structures particularly susceptible to growth retardation are the skin and its appendages, lymphoid organs and mesenchymal tissue.[324] The local application of cortisone to these tissues reduces or even halts further growth, suggesting that the hormone exerts a direct cellular action on growth processes in addition to an indirect effect consequent to the induction of a negative nitrogen balance.[7] A suppression of mitotic activity in the skin epithelium of mice followed both parenteral and local administration of cortisone acetate.[325] DeRopp[326] has shown that the capacity of the hormone to suppress growth extends even to certain plant tumors. That growth inhibition is of more than academic interest, however, is indicated by reports of a suppression of growth in children with Cushing's syndrome,[327] in premature infants during intensive corticotropin therapy[328] and in infants with congenital adrenal hyperplasia during treatment with cortisone.[329]

Of particular interest are the numerous studies establishing the capacity of cortisone to inhibit, at least temporarily, the growth of certain tumors. Neoplasms demonstrated to be susceptible to suppression include transplantable lymphosarcomas in mice,[330] skin carcinomas induced in mice by methylcholanthrene,[331] the Walker carcinoma in rats,[332] transplanted rhabdomyosarcomas in mice[333] and osteogenic sarcomas in mice.[334] In almost all cases tumors eventually recurred and became refractory to further treatment. In man cortisone has produced regression of lymphomatous tumors including lymphosarcoma, leukemia, Hodgkin's disease and, in occasional cases, plasma cell myeloma.[143] Unfortunately, the neoplastic process recurs when treatment is withdrawn and response to further therapy is usually diminished or lacking. Furthermore, therapeutic results after cortisone administration, even in these relatively susceptible forms of tumor, are unpredictable. This implies a peculiar therapeutic specificity that has been interpreted as evidence for the existence of multiple etiologic factors. Hence it is possible that the results of steroid therapy are largely determined by both the intrinsic biologic nature of the cells affected and the metabolic alterations produced in the environment of those cells, rather than by an effect upon neoplastic growth in general.[335]

The administration of large doses of cortisone to pregnant mice has been found to result in a surprisingly high incidence of cleft palate in the offspring.[336] In view of the fact that the defect could be produced after the period when the nasomaxillary fissure normally closes, the authors suggested that the defect was degenerative rather than a consequence of delayed development. In view of the comparatively immense doses of hormone used, it is not possible to transfer the implications of these experiments to the thera

peutic use of cortisone in human pregnancy[337] Nevertheless the data are of great interest in relation to the problem of etiologic factors in the development of congenital defects

Effects upon Mechanisms of Defense The capacity of the organism to respond to stress is profoundly modified in the presence of a deficiency or excess of adrenocortical hormones Vulnerability to exogenous stress is the predominant characteristic of patients with Addison s disease equally striking is the marked protection from ordinary levels of stress that relatively small quantities of 11 17 oxysteroids such as cortisone afford These stable doses of hormone do not however permit the flexibility of response to varying grades of stress enjoyed by the person with intact adrenal glands Indeed this mobilization of adrenocortical steroids in response to exogenous stress forms the basis of Selye s challenging concept of the processes of adaptation[275] This concept embracing the sum of the systemic reactions of the body that follow exposure to stress has succeeded in emphasizing the central role of pituitary adrenal activation in the mechanisms of nonspecific resistance Continuous overactivity of this system (Cushing s disease) however may profoundly alter the reactions of the organism to certain forms of stress particularly infection and trauma indicating a potent influence of adrenal steroids on processes of inflammation and the reparative capacity of the mesenchymal system That a state of induced hyperadrenocorticism may likewise influence these processes has become increasingly evident in this era of extensive investigation of the experimental and therapeutic applications of adrenocortical hormones

The original observations of Hench et al[10] on the dramatic effect of cortisone and corticotropin upon rheumatoid arthritis served to call attention to the capacity of adrenocortical hormones to suppress the processes of inflammation This suppression was evidenced clinically by a rapid lessening of the classic signs of inflammation and histologically by a decreased number of plasma cells and lymphocytes a reduction of papillary tufting a decreased deposition of fibrin and diminution of necrosis and edema in the synovial membrane These historic observations have been confirmed in numerous studies in which cortisone has been shown to be capable of suppressing the inflammatory response to a wide variety of inciting agents including chemical irritants[338 339] foreign protein[340 341] and microorganisms[34 343]

In a detailed study of the tissue response to the subcutaneous injection of histamine in adrenalectomized mice Dougherty[344] found the intensity of inflammatory reaction to be reciprocally proportional to the amount of cortisone or hydrocortisone available in the inflamed area The hormones effectively inhibited the destruction of fibroblasts and the invasion of polymorphonuclear leukocytes and macrophages Rebuck et al[345] employing the skin window technic in man studied the effect of adrenocortical stimulation upon the inflammatory reaction to foreign proteins (ovalbumin and tuberculin) As a consequence of hormonal therapy there was an inhibition of lymphocytic hypertrophy and migration resulting in a relative predominance of neutrophils and histiocytes The effect of intramuscularly injected cortisone

upon the local inflammatory response to cutaneous and testicular pneumococcal infections in rabbits has been described by Germuth and his associates.[346] In control animals there were numerous neutrophilic leukocytes, necrosis and thrombosis of small vessels, hemorrhage, and edema. In treated animals the leukocytic response was definitely suppressed, the blood vessels were normal, and the number of viable bacteria was greatly increased. Since the number of circulating neutrophils increased, the paucity of these cells at the inflammatory site was considered to be the consequence of an interference with cellular migration. The capacity of the inflammatory process to limit the spread of infection was clearly diminished during cortisone administration and an intensification of bacteremia occurred. In view of the possible production of hyaluronic acid by mast cells, it is of interest that in several species, including man, the number of these cells in cutaneous connective tissue declined during the administration of cortisone.[347]

The studies of Ebert and Barclay[348] utilizing the ear window technic in rabbits have emphasized the changes produced by parenterally administered cortisone on the vascular component of the focal inflammatory response to tuberculin. In untreated animals the reaction was associated with an increased sticking of leukocytes to vascular endothelium, lability of the circulation evidenced by alternating periods of vasoconstriction and dilatation, hemoconcentration, stasis, and vascular thrombosis, and increased exudation and liquefaction of caseous material. The effective suppression of these changes by cortisone was considered to be the result of a preservation of vascular tone and endothelium. Menkin[349] has also demonstrated by dye diffusion studies a reversal of the enhanced capillary permeability associated with acute inflammation.

It is clear, therefore, that cortisone exerts a suppressive effect upon the basic processes of inflammation. Vascular permeability is decreased, exudation diminished, and the migration of inflammatory cells materially impaired, resulting in an over-all reduction in local phagocytic activity. Consequently, the classic signs of acute inflammation are lessened and the spread of microorganisms facilitated. Furthermore, reparative processes may be inhibited by virtue of the potent effects upon the reactivity of other mesenchymal elements. Cortisone affects all components of connective tissue, resulting in a decrease of fibroplasia and a shrinkage of collagenous fibers. These changes are reflected in delayed wound healing. Intensification of hormone activity leads to a disorganization of the reticulum and probably results in an inhibition of heteroplastic differentiation of lymphocytes[350] and a curtailed production from parent reticulum of all types of phagocytic cells.[25]

The inhibitory effects of cortisone upon the manifestations of infectious and inflammatory disease are not confined to the local processes of inflammation. The systemic manifestations, such as fever and signs of toxemia, may also be suppressed. This apparently beneficial alteration in the reaction of the host is illusory, however, because the etiologic agent remains unaffected by the hormone. The now classic example of this phenomenon is the striking

but temporary suppression of the manifestations of rheumatoid arthritis The perforation of a viscus without signs of peritonitis and the dissemination of infection without signs of septicemia are extreme and potentially dangerous, examples of the same phenomenon The exacerbation of tuberculosis during cortisone administration deserves special emphasis Numerous reports on the aggravation of experimental tuberculous infection in animals have appeared[351] and a growing clinical experience has confirmed these observations in man [35] It is strongly recommended therefore that cortisone and corticotropin should not be used in patients with active tuberculosis and should be employed only with considerable caution in patients with latent or inactive disease

The dramatic effects of cortisone and corticotropin upon diseases known or assumed to be of allergic origin have stimulated extensive investigation of the influence of these hormones on the humoral mechanisms of defense An extensive literature has appeared that is highly complex often conflicting and difficult to interpret Recently however certain trends have emerged based on meticulous well controlled studies which promise eventual clarification

The report of Dougherty Chase and White [353] in 1945 called attention to the possible relation between adrenal hormones and antibody formation Evidence was presented that the administration of corticotropin to immunized rabbits resulted in a liberation of antibodies from lymphoid tissue Subsequent workers however [354 355] were unable to detect a significant rise in antibody titer under these conditions In addition numerous studies in man failed to demonstrate an effect of cortisone upon circulating antibody titers [40 356] or upon the production of antibodies in response to specific sensitization [3 7] However more recent experimental studies in animals employing careful quantitative immunologic techniques have indicated that these hormones are not without effect on serum antibody levels Bjørneboe et al [358] and Germuth[359] have demonstrated a significant inhibition of the rise in antibody titers following specific sensitization during the administration of cortisone and corticotropin Moreover the hormones failed to alter the rate of disappearance of antibody in passively immunized animals It was concluded that the predominant effect of cortisone and corticotropin was an inhibition of antibody synthesis The observations by Germuth and his co-workers[359] of a marked suppression of the *active* phenomenon of Arthus during hormone administration and the failure of Fischel[360] to inhibit the local *passive* Arthus reaction are consistent with this view On the other hand the occasional observations of a marked decline in antibody level after only a few hours of cortisone or corticotropin administration[361] indicate in view of a demonstrated half life of antibody protein of approximately 14 days [36] that an alteration in distribution or acceleration of antibody degradation may also be involved

It is generally considered that cortisone is incapable of inhibiting the union of antigen and antibody This view is based on the failure of most workers to prevent anaphylaxis in various species In addition it has been

observed that cortisone may block actively induced nephrotoxic nephritis (bovine gamma globulin [363] and horse serum[356]), where is the passively induced disease (kidney antiserum) is not prevented [77] In the former an interference with antibody production undoubtedly occurs [364] but a suppression of tissue reactivity by the hormone may also be involved [35] It should be pointed out that in a few experiments[366 367] acute anaphylaxis has been successfully prevented This has occurred with comparatively large doses of the hormone, and it has been assumed that a block in tissue response is involved [334]

The resemblance between the pharmacologic effects of histamine and the manifestations of acute anaphylaxis has led to the suggestion that antigen antibody union may provoke a release of histamine or histamine like substances[368] from the tissues A number of studies indicate that intense adrenocortical stimulation does not significantly alter the ability of tissue to release histamine like substances or to respond to either these substances or histamine itself [369] It is unlikely therefore that the therapeutic effectiveness of cortisone in allergic states is related to an interference with these mechanisms

The effects of cortisone and corticotropin upon certain local allergic phenomena have also been investigated An inhibition of the tuberculin reaction by comparatively large doses of the hormones has been reported by Long and Favour [370] Stoerk [371] and others Kabat[372] has observed a suppression of allergic encephalomyelitis in animals It is generally agreed that the Shwartzman phenomenon may also be effectively blocked [373] It appears that the effects of the hormones in these phenomena depend upon an interference with some phase of tissue reactivity

There is no doubt that cortisone and corticotropin may favorably modify the course of a variety of diseases of hypersensitivity in man such as allergic dermatitis [374] bronchial asthma[375] and hay fever [376] The actual site of action is not clearly understood Fischel[364] has recently discussed the potential implications of the experimental observations cited above to the mode of action of these hormones in human allergic disorders It was emphasized that although it has been clearly demonstrated that antibody synthesis is depressed by cortisone the depression is small in extent and occurs only when extraordinarily large quantities of the hormones are employed That the antibody effect is probably not of major importance in the therapy of *allergic states is evident in patients with asthma or hay fever* whose symptoms may be adequately controlled by cortisone but in whom sufficient reagin or antibody is present to give satisfactory skin reactions Fischel concludes that the clinical efficacy of cortisone probably bears little relation to antibody inhibition except in certain specific disorders such as acquired hemolytic anemia in which clinical improvement usually coincides with a disappearance of abnormal antibodies from the blood

In summary it is apparent that cortisone and corticotropin are capable of suppressing the local and systemic response of the organism to a wide variety of inciting agents It is probable that the mechanism of action of these hormones on the hypersensitive state is fundamentally similar to their effect upon the inflammatory response of connective tissue In all likelihood

the common factor in the multiple actions of cortisone and corticotropin on the bodily mechanisms of defense is a modification of the reactivity of mesenchymal tissue

Toxicity

Cortisone is either a natural secretory product of the adrenal cortex or a potent metabolically active adrenal steroid derivative It is to be expected therefore that the undesirable effects that may follow its clinical use would be of two general types those due to overdosage of the hormone, representing an exaggeration of its physiologic actions and occurring during intensive and prolonged administration and those occurring chiefly after hormone withdrawal reflecting a state of adrenal insufficiency induced by hormonal suppression of adrenocortical function The former effects are epitomized in the patient with classic Cushing s syndrome the latter exemplify the major metabolic defects of patients with Addison s disease

It is to be emphasized that the dose of cortisone ordinarily employed in nonspecific clinical therapy is different from the quantity of hormone normally secreted by the adrenal cortex Although it has been suggested that the therapeutic action of cortisone may depend upon the correction of a state of relative adrenal hormone deficiency at the local site of disease there is no doubt that to achieve a therapeutic effect one must definitely exceed the well delineated dosage of cortisone required in the maintenance therapy of patients with adrenal insufficiency Indeed the very basis of successful steroid therapy appears to be the controlled induction of a state of hormone overdosage Thus it is inevitable that effective cortisone therapy will be associated with significant alterations in the normal pattern of metabolic reactions Initially these alterations are effectively offset by the compensatory mechanisms of homeostasis With continuing hormonal therapy however the capacity of these mechanisms may be exceeded and overt manifestations of overdosage may appear at first on a biochemical plane and eventually on a structural level It should be pointed out that certain conditions predispose to the development of specific overdosage phenomena at dosage levels that are incapable of inducing the entire picture of Cushing s syndrome Pertinent examples include the production of frank diabetes in patients with latent diabetes the exacerbation of a quiescent peptic ulcer the aggravation of hypertension in the presence of renal damage and the development of osteoporosis in immobilized patients Both the biochemical and the structural changes associated with prolonged cortisone administration have been discussed in detail in the earlier section on physiologic actions Fortunately the majority of these changes can be prevented or minimized by specific measures and with few exceptions they completely disappear after discontinuation of therapy

In contrast to the manifestations of hormone excess that appear *during* cortisone administration symptoms of hormone deficiency occur with either a drastic reduction in dosage or the abrupt cessation of the drug These symptoms may be mild or severe depending upon the duration of therapy

level of dosage and rapidity of hormone withdrawal After prolonged treatment even with moderate doses of cortisone, a profound depression of adrenocortical function may ensue In some patients the clinical manifestations of adrenal insufficiency may continue for a protracted period, in unusual cases this state may persist for as long as 60 to 90 days The advent of adrenal insufficiency particularly if it is accompanied by either a violent relapse of the disease for which hormonal therapy was instituted or by an intercurrent stress, such as infection or trauma may prove disastrous Fortunately serious manifestations of adrenocortical insufficiency associated with cortisone withdrawal may be minimized by a gradual tapering of hormone dosage and the concomitant stimulation of the adrenal gland with corticotropin

In addition to the precipitation of adrenocortical insufficiency by the sudden cessation of cortisone therapy a state of relative hypoadrenocorticism may develop during the course of therapy as a consequence of superimposed stress Under these circumstances it is assumed that the adrenocortical atrophy secondary to long continued therapy prevents or modifies the capacity of the gland to increase its secretion of hormone The susceptibility of patients to superimposed stress in the presence of what would ordinarily be an adequate quantity of circulating hormone is no doubt conditioned by the adaptation of the organism to the continued administration of high doses of hormone A state of relative adrenal insufficiency after the sudden imposition of stress may even occur in a patient who because of prolonged cortisone therapy exhibits clinical manifestations resembling those of Cushing's syndrome In these circumstances additional cortisone should be given

Procedures Required during Therapy Certain procedures should be carried out in all patients who are candidates for *prolonged* cortisone therapy In the first place in view of the potential aggravation of active tuberculosis by cortisone X ray examination of the lungs is advised In the presence of active tuberculous disease treatment with cortisone acetate should be withheld except as substitution therapy in patients with Addison's disease Should inactive lesions be discovered hormonal therapy may be instituted but periodic reexaminations are indicated Secondly a history suggestive of peptic ulcer warrants roentgenographic examination of the upper gastrointestinal tract In the presence of an active ulcer the administration of cortisone is contraindicated If a deformity indicative of a healed lesion is discovered hormonal therapy may only be undertaken if the indications for its use are carefully evaluated and accepted measures for ulcer management are instituted Thirdly a urinalysis for the presence of glucose should be performed In the presence of a strong family history of diabetes both a fasting and a postprandial blood sugar determination should be made Neither *latent nor overt* diabetes mellitus contraindicates cortisone therapy However in their presence periodic blood sugar measurements and routine urine tests are indicated Finally the basal blood pressure should be determined An elevated level even in the presence of renal disease does not prohibit the therapeutic use of cortisone but does indicate the necessity for frequent blood pressure measurements throughout therapy

The use of cortisone in patients with heart disease is a problem requiring careful medical judgment in individual cases Neither severe though well compensated cardiac disease nor heart failure that is satisfactorily controlled by medical therapy contraindicates treatment with the hormone in these cases, however one must take particular care to prevent both excessive sodium and water retention and potassium loss Intractable heart failure is a contraindication to cortisone therapy unless it is caused by a condition that may be alleviated by the hormone e g acute rheumatic carditis

A low salt diet and supplementary potassium administration are routine measures that should always accompany prolonged cortisone treatment Sodium restriction minimizes but does not entirely eliminate urinary potassium loss[15,377] in a manner comparable to that described for DOC A high potassium intake on the other hand materially reduces sodium retention[378] These measures therefore will largely offset the development of edema due to sodium and water retention and the muscular weakness and hypokalemic alkalosis caused by potassium depletion A few relatively simple measures facilitate the detection of the common manifestations of overdosage[379] Body weight should be determined daily If weight gain and edema ensue rigorous salt restriction should be instituted and if necessary diuretic agents should be administered Potassium depletion may be evidenced by skeletal muscle weakness characteristic electrocardiographic changes an increase in serum carbon dioxide combining power and a decrease in serum chloride and potassium levels (hypokalemic alkalosis) The development of significant potassium depletion however is unusual in the presence of an adequate diet and a daily supplement of 1 to 3 Gm of a potassium salt Periodic urinalyses for the presence of glucose should be performed Glycosuria in the absence of a significant degree of hyperglycemia may be ignored If a marked degree of hyperglycemia develops insulin therapy should be instituted

Possible Complications of Therapy The remaining common complications of cortisone therapy can be detected by careful clinical observation Rounding of the face is a sensitive and early sign of overdosage Characteristic changes in fat distribution as seen in Cushing s syndrome likewise may occur relatively early Acne mild hirsutism and eventually cutaneous striae may appear A suppression of menses and changes in libido are not infrequent These manifestations do not contraindicate continued hormonal therapy

The major complications of intensive cortisone therapy are few but of serious import The development of symptoms and signs of peptic ulceration constitutes an absolute contraindication to the continuation of therapy owing to the danger of perforation and massive hemorrhage One should be constantly alert for the development of intercurrent infection since hormonal therapy may effectively attenuate the inflammatory manifestations of infection without affecting the etiologic agent If the causative organism is known and an effective antibiotic is available hormonal therapy need not be discontinued On the other hand if effective control of the infectious agent is not possible, continuation of cortisone therapy may prove extremely hazard-

ous One must be particularly alert for the development of a severe degree of osteoporosis with its attendant hazard of pathologic fracture in patients long immobilized or in whom osteoporosis already exists (as in postmenopausal women) In these cases the maintenance of a high protein intake and the administration of testosterone may at least partially counteract the antianabolic effects of cortisone A serious interference with wound healing rarely occurs unless the dosage is high (greater than 150 mg a day) and prolonged, and protein intake is inadequate Growing experience indicates that the vast majority of fractures traumatic wounds and operative incisions heal satisfactorily despite concomitant cortisone administration Accumulating reports suggest that an increased incidence of thromboembolic phenomena may be associated with cortisone therapy particularly during the period immediately after withdrawal It appears that the presence of chronic liver disease may predispose to the development of this complication Rarely signs of vascular fragility such as easy bruisability and purpura may become severe enough to require a reduction in dosage Convulsive seizures occasionally occur being seen predominantly in patients with disorders of the central nervous system In these cases either a reduction of the dose or institution of anticonvulsant therapy is indicated

In the present state of knowledge it appears impossible to predict accurately which patients may manifest severe mental symptoms during cortisone therapy Mild euphoria or less commonly mild depression and moderate mental and physical hyperactivity do not in themselves necessitate discontinuation of therapy A marked progression of these symptoms or the appearance of certain warning sign such as pronounced paresthesias uncontrolled thoughts and mental confusion may presage the development of serious aberrations of affect or behavior and require immediate cessation of treatment

The need for meticulous care in withdrawal of cortisone after prolonged therapy has already been emphasized Dosage should be tapered off gradually e g 12 5 to 25 mg a day at intervals of two to seven days especially if the hormone has been given by the oral route During the period of withdrawal corticotropin should be administered until normal levels of endogenous adrenocortical secretion are restored Either the intravenous infusion of corticotropin or the intramuscular injection of a potent long acting preparation of corticotropin is particularly effective

Absorption Intermediary Metabolism and Excretion

Absorption One of the earliest indications that adrenocortical hormones might be absorbed from the gastrointestinal tract came from a report by Osler[380] in 1896 of a patient with Addison s disease who appeared to improve after the oral administration of a glycerol extract of hog adrenal glands In 1931 Britton and Silvette[381] clearly demonstrated that orally administered adrenocortical extract could serve as adequate substitution therapy in adrenalectomized cats That cortisone itself might be absorbed from the gastrointestinal tract was first indicated by Freyberg [382] who reported the

effectiveness of oral administration of this hormone in the treatment of rheumatic disease. This view was amply confirmed in many reports describing the oral use of cortisone in a variety of conditions and by the metabolic studies of Thorn et al.[250] in man. Thorn and his associates compared the effects of cortisone given by the oral and intramuscular routes upon the circulating eosinophils, urinary sodium, potassium and chloride excretion and thyroid and adrenocortical activity. It was found that orally administered cortisone reproduced the complete spectrum of metabolic actions of intramuscularly administered cortisone. Its action, however, was more rapid and evanescent. It thus appears that the hormone is rapidly absorbed from the gastrointestinal tract, whereas absorption from an intramuscular depot is slow and prolonged. A further illustration of the different rates of absorption of orally and intramuscularly given cortisone has come from studies of the levels of plasma 17-hydroxycorticosteroids after the administration of the hormone by the two routes. Nelson et al.[383] observed that the oral administration of 200 mg. of cortisone as either the acetate or the free alcohol led to a prompt rise in plasma 17-hydroxycorticosteroids with a peak at approximately one hour and a gradual return to control levels in four to eight hours. A similar response was seen when the free alcohol was given in ethanol solution by a single intramuscular injection. When 200 mg. of cortisone acetate was administered intramuscularly in saline solution, however, little or no elevation of plasma 17-hydroxycorticosteroid levels occurred.

The pathway of absorption of cortisone from the gastrointestinal tract is unknown. The findings of Chaikoff et al.[384] that in the rat cholesterol is absorbed almost exclusively via the intestinal lymphatics and thence travels through the thoracic lymph duct to the systemic circulation suggest that it may not be correct to assume that the bulk of cortisone that has been absorbed from the intestine passes via the portal vein to the liver.

Intermediary Metabolism. No studies of the distribution of administered cortisone in the mammalian organism have been reported. Studies of this kind depend upon the availability of isotope labeled hormone. At present the synthesis of C^{14} labeled cortisone is being actively pursued and the results of metabolic studies with this material are eagerly awaited.

The biosynthesis of cortisone from acetate has been demonstrated in hog adrenal slices incubated with C^{14} acetate[385] and in beef adrenal glands through which radioactive acetate has been perfused.[4] The hormone has also been isolated from normal human urine.[3, 6, 37] It has not, however, been detected in the adrenal venous blood[388] or the peripheral blood[389] of animals. It is of interest that cortisone has recently been isolated from the human placenta, suggesting that synthesis of the hormone may occur in this organ.[390]

One cannot be certain from these observations that cortisone is a primary secretory product of the mammalian adrenal gland. Indeed, the finding that hydrocortisone (compound F) is the principal corticoid in adrenal gland perfusates,[4] adrenal venous blood[388, 391] and peripheral blood[389] has led to the view[39] that cortisone is either a precursor or a metabolite of the principal adrenal product, compound F.

There is strong evidence that circulating cortisone undergoes rapid removal from the blood stream and inactivation in the tissues. After the intravenous infusion of cortisone in dogs, Nelson et al[393] observed that 90 per cent of the hormone disappeared from the circulation within 10 minutes. Studies of arteriovenous differences in 17-hydroxycorticosteroid levels after the intravenous injection of cortisone revealed a definite transformation of the hormone in liver but not in muscle or kidney.[394] Hechter[39] likewise reported the rapid disappearance of cortisone perfused through rat liver. Paschkis and his co-workers[396] incubated cortisone with various tissues of the rat and assayed the remaining hormone by the mouse glycogen-deposition method. They found that tissues such as muscle and brain were just as effective as liver in inactivating the hormone. With similar technics Louchart and Jailer[397] demonstrated over 70 per cent transformation of cortisone after a three hour incubation with mouse liver, kidney and spleen slices, blood, serum and slices of muscle and brain however did not appreciably inactivate the hormone. A detailed investigation of the effects of incubation of cortisone with a variety of surviving rat tissues has recently been reported by Schneider and Horstmann.[398] The hormone was added to minces and slices of liver and kidney, to adrenal homogenates and to slices of diaphragm and heart muscle. The metabolism of the steroid was studied with the aid of ultraviolet spectrophotometry, paper chromatography and the Porter-Silber[399] and periodate oxidation assays. It was observed that only liver and, to a lesser extent, kidney caused a rapid reduction of the α, β unsaturated ketone grouping in ring A (Figure 12) and extensive degradation of the side chain at C 17. That the liver also plays an important role in the transformation of cortisone to 17-ketosteroids is indicated by the finding of Butt et al[400] that less administered cortisone was converted to 17-ketosteroids in patients with hepatic disease than in patients without demonstrable liver damage.

Excretion. No studies on the excretion of cortisone or its metabolites in feces have been reported. It is not known whether cortisone may be completely oxidized to water and carbon dioxide, which would then appear in the expired air; only when isotope labeled hormone becomes available can this question be answered.

The bulk of knowledge concerning the metabolic fate of cortisone has come from studies of steroids in urine, chiefly in man. It is well known that in patients with Addison's disease the administration of cortisone leads to an increase in the urine of 17-ketosteroids and steroids with an α-ketol side chain at C 17 (formaldehydogenic steroids[401] and reducing corticosteroids[402, 403]) (Figure 12). Similar findings are obtained in subjects with intact adrenal glands provided the dose of cortisone is sufficiently high.[116] With smaller doses of the hormone (50 to 100 mg. daily) the administration of cortisone may be followed by a fall in the 17-ketosteroid values, particularly if the initial levels of urinary 17-ketosteroids are normal or high. It is believed that this fall indicates a suppression of endogenous adrenocortical secretion and that the 17-ketosteroids excreted during the administration of a "suppressive" dose are derived largely, if not entirely, from the cortisone adminis-

tered This belief is supported by the observation that under these conditions the specific 17 ketosteroids androsterone and etiocholanolone, which are ordinarily found in urine and which, in women, are solely derived from the adrenal cortex, cannot be detected It should be noted that after the admin

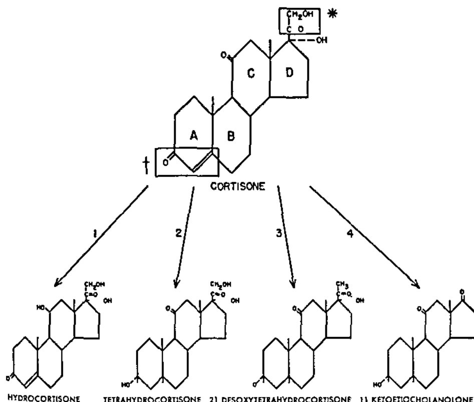


FIG 12 Pathways of cortisone metabolism

* = α ketol side chain at C 17

† = $\alpha\,\beta$ unsaturated ketone group in ring A This figure represents examples of the major metabolic changes that cortisone undergoes *in vivo* 1 = Reduction at C 11 2 = Reduction of the $\alpha\,\beta$ unsaturated ketone group in ring A the formation of tetra hydrocortisone involves the addition of two hydrogen atoms at C 3 and a single hydrogen atom at C-4 and C 5 with saturation of the 4–5 double bond 3 = Reduction of the $\alpha\,\beta$ unsaturated ketone group in ring A with partial degradation of the side chain at C 17 4 = Reduction of the $\alpha\,\beta$ unsaturated ketone group in ring A with complete degradation of the side chain at C 17 and the formation of 17 ketosteroids

istration of small doses of cortisone to human subjects with intact adrenal glands the magnitude of the rise in urinary 17 ketosteroids and α ketolic corticoids is variable and may not be maintained during long continued hormonal therapy

The major portion of both the 17 ketosteroids and α ketolic corticoids of normal urine and the urine of human subjects who have been given cortisone appears to be conjugated as glucuronides and ethereal sulfates [404] A small proportion of these steroids may be conjugated in a manner as yet un

known.[405] The rise in urinary 17-ketosteroids following cortisone administration is largely due to an increased excretion of three 11-oxysteroids: 11-ketoetiocholanolone, 11β-hydroxyetiocholanolone, and 11β-hydroxyandrosterone.[406–408] There is no discernible increase in the output of such steroids as androsterone or etiocholanolone which lack the C-11 oxygen. Indeed, the loss of the oxygen at C-11 during the metabolism of cortisone has not yet been demonstrated. It is believed that the adrenal precursors of the 11-desoxy 17-ketosteroids are hormones that do not initially possess an oxygen atom at C-11, such as 11-desoxy-17-hydroxycorticosterone (compound S) and 17-hydroxyprogesterone. This belief is supported by the demonstration that the administration of the latter substances labeled with radioactive carbon leads to the excretion in the urine of radioactive androsterone and etiocholanolone.[408]

It is well known that the administration of large doses of cortisone in female patients may induce acne and hirsutism. Recent experiments[409] in this laboratory indicate that in man cortisone causes urinary excretion of substances that possess biologic androgen activity. Patients who had undergone bilateral orchiectomy and bilateral complete adrenalectomy for metastatic carcinoma of the prostate were given varying doses of cortisone by mouth and specimens of urine were assayed for androgenic activity by the chick comb method. It was observed that although androgen excretion was proportional to cortisone dosage and roughly paralleled the level of urinary total neutral 17-ketosteroids, even at a dose of 300 mg. a day the level of urinary biologically active androgens was lower than that in a normal man. In addition, the quantity of androgens derived from a given dose of cortisone was somewhat lower than that obtained with hydrocortisone but higher than that seen with corticosterone.

The principal α-ketolic corticoid in normal urine[387, 410] and in the urine of human subjects who have been given cortisone[410] has been identified as tetrahydrocortisone (pregnane-3α,17α,21-triol-11,20-dione). (See Figure 12.) Studies with this compound in man have failed to demonstrate any metabolic activity.[4] Tetrahydro-hydrocortisone (pregnane-3α,11β,17α,21-tetrol-20-one),[408] dihydrocortisone (pregnane-17α,21-diol-3,11,20-trione),[387] cortisone and hydrocortisone[386, 387, 405, 410–412] have also been separated from the α-ketolic fraction. *The presence of the reduction products, i.e.*, tetrahydrocortisone, tetrahydro-hydrocortisone, and dihydrocortisone, indicates that one of the metabolic transformations of cortisone *in vivo* involves partial or complete saturation of the α,β-unsaturated ketone grouping in ring A. It is interesting that in normal human urine and in the urine of subjects who have received cortisone[387, 410] the proportion of the urinary tetrahydrocortisone existing as a glucuronide conjugate is much higher than that of the urinary cortisone. These observations suggest that the reduction of cortisone to tetrahydrocortisone facilitates glucuronide conjugation. The possibility that cortisone and hydrocortisone are excreted in part as non-17-hydroxylated α-ketols must be considered.

That partial transformation of the side chain at C-17 may occur during

the metabolism of cortisone has been shown by the isolation of 21 desoxy-tetrahydrocortisone (pregnane-3α 17α diol 11 20 dione) from the urine of patients receiving cortisone[408] (Figure 12) There is also evidence that reduction of the C 20 ketone group with production of steroid glycols occurs[406]

The major metabolic transformations of cortisone *in vivo* may be summarized as follows the hormone may be excreted unchanged it may undergo reduction at C-11 with the formation of hydrocortisone (Pathway 1 Figure 12), there may be partial or complete reduction of the α β unsaturated ketone grouping in ring A with the formation of dihydrocortisone tetrahydrocortisone and tetrahydro-hydrocortisone (Pathway 2 Figure 12), partial degradation of the side chain at C 17 may occur with the formation of 21 desoxytetrahydrocortisone (Pathway 3 Figure 12) and there may be complete degradation of the side chain with the formation of 17-ketosteroids (Pathway 4 Figure 12) which appear to retain the oxygen atom at C 11 It is to be noted that whereas the reduction of the α β unsaturated ketone grouping in ring A of cortisone may take place without further catabolism of the steroid, this change must proceed or accompany any metabolic alteration in the side chain at C 17[413] It appears likely that the metabolic products of cortisone are excreted for the most part as conjugates of glucuronic and sulfuric acids Finally the need for further development of this complex field is emphasized by the knowledge that the greater part of administered cortisone disappears and is unaccounted for by the sum total of known metabolites

Preparations and Routes of Administration

Cortisone is supplied for therapeutic use in the form of the acetate ester Four preparations are currently available tablets for oral administration containing 5 or 25 mg of cortisone acetate for intramuscular injection a microcrystalline suspension of cortisone acetate in physiologic saline solution containing 25 or 50 mg per cc (minute quantities of suspending agents such as polyoxyethylene sorbitan mono oleate and sodium carboxymethylcellulose and a preservative such as 0 9 per cent benzyl alcohol are also present) a microcrystalline suspension of cortisone acetate in a solution of phosphate buffer for ophthalmic (topical) use containing 5 or 25 mg per cc with suitable preservative and two ophthalmic ointments with 1 5 per cent concentration of cortisone acetate in petrolatum base one of which also contains 1 000 units of bacitracin per Gm

Solutions of cortisone suitable for continuous intravenous administration have recently been prepared in this laboratory[413] the nonacetylated (free alcohol) compound being used since it has not been possible to date to prepare a satisfactory solution of cortisone acetate for intravenous use The following method of formulation has been employed a sterile aqueous suspension of cortisone (*free alcohol*) containing 25 mg per cc is added to sterile 95 per cent ethyl alcohol and sterile water in the order given in the proportions of 4 cc of steroid suspension, 6 cc of alcohol and 4 cc of water This solution is immediately diluted to any desired volume in physiologic

saline solution or 5 per cent dextrose in water for intravenous infusion. If aqueous suspensions of the steroid are unavailable, satisfactory solutions may be prepared from crystalline cortisone, a known quantity of sterile cortisone (*free alcohol*) being dissolved by vigorous shaking in 80 per cent ethyl alcohol in the proportions of 10 mg per cc. This solution is then injected *rapidly* into the desired volume of saline or dextrose diluent for intravenous infusion. No untoward effects have been observed from the relatively small quantity of alcohol used. The administration of 100 mg of *cortisone dissolved in 500 cc of saline or dextrose solution by continuous* intravenous infusion over a period of eight hours or longer has been demonstrated to produce metabolic changes of nearly maximal intensity.[434]

Cortisone is ordinarily administered for therapeutic purposes by either the intramuscular or the oral route. In addition, the hormone has been infused intravenously, dropped into the conjunctival sac and injected directly into accessible body spaces, including joints, bursas and the pleural, peritoneal and pericardial compartments. The hormone has been rubbed onto the skin in ointments and solutions, implanted under the skin in the form of pellets and sprayed into the upper respiratory tract as an aerosol. Such a diversity of routes reflects the attempt to modify, largely by restriction of hormonal activity to specific areas, *the generalized metabolic effects* obtained with systemic administration.

The first preparation of cortisone available for general clinical use was the microcrystalline suspension in physiologic saline solution for intramuscular injection. Dissolution of the intramuscular deposit of steroid crystals proceeds so slowly that the blood levels of free corticosteroid are usually only moderately elevated.[343] Consequently, the effective duration of a single dose ordinarily extends over a period of 24 hours or slightly longer. Although the peak activity of a single dose usually occurs between 8 and 12 hours after intramuscular injection, both metabolic and clinical effects are often evident within 3 or 4 hours. To obtain a rapid and sustained level of maximal activity, the hormone is ordinarily administered at intervals of 8 to 12 hours; for maintenance therapy, however, a single injection during each 24 hour period is ordinarily sufficient. After prolonged intramuscular administration of large doses of cortisone acetate, cumulation of the hormone is evidenced by a persistence of effects for several days after the discontinuation of injections.

It has repeatedly been demonstrated in man that the over-all metabolic and therapeutic effects of equivalent daily doses of orally and intramuscularly administered cortisone acetate are not strikingly different. The clinical dosage equivalence ratio of orally to intramuscularly given hormone has in most cases *ranged between 1.0 and 1.5*.

The effects of cortisone acetate given intramuscularly and by mouth differ chiefly *in their time response relations*. This is well illustrated by a comparison of changes in circulating eosinophils elicited by single doses of the hormone in patients *with Addison's disease*, *in* whom variations in endogenous corticosteroid secretion do not influence the evaluation of re-

sults The maximal effect of cortisone by mouth is ol eight hours and rapidly declines thereafter In cont action of intramuscularly injected cortisone acetate i not only much less intense but also markedly delayed a slow absorption rate Even with continued daily int of 100 to 200 mg eosinopenia may not be pronounced actions of the intramuscular depots become apparent

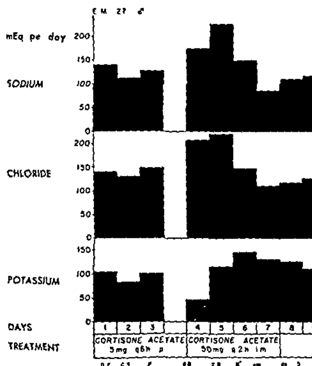


FIG 13 Comparison of effect of oral and intramuscular sone upon renal excretion of electrolyte The periods of administration were consecutive (Reproduced from Thorn

Similar differences between the two routes are well parison of the effects upon urinary electrolyte excretion of intramuscularly and orally administered cortisone with Addison's disease (Figure 13) Upon substitut cortisone acetate for an equivalent total daily dose o hormone a prompt rise in sodium and chloride excre fall in urinary potassium indicated rapid disappearanc oral preparation In addition the onset of effective el delayed until the third day of intramuscular administ persisted through the fifth day after the last injection o

appears however that the intramuscular preparation is somewhat more effective in its electrolyte regulating capacity, once maximal activity is reached, than the orally administered hormone It is probable that this difference is attributable to the sustained effect upon renal function of a relatively slow but continuous absorption of cortisone

A further disparity between the effects of oral and intramuscular administration of the hormone deserves emphasis Wilkins et al [81] have well demonstrated that intramuscularly injected cortisone acetate, despite a delay in onset of action is considerably more efficient than an equivalent quantity of steroid administered orally in the suppression of adrenocortical activity in patients with congenital adrenal hyperplasia Experience in this clinic indicates that this finding applies equally well to patients with normal adrenocortical function These observations suggest that the release of cortisone acetate from intramuscular depots more effectively inhibits the output of corticotropin from the anterior pituitary body than the intermittent activity of orally administered hormone It seems evident that differences in time response relations between these two systemic routes of hormone administration as well as quantitative differences in certain metabolic actions, can be attributed to the marked disparity occurring in the rate of absorption of the hormone

It is therefore apparent that the oral use of cortisone acetate in clinical therapy requires frequent administration In most cases the therapeutic effectiveness of cortisone acetate given orally at six hour intervals is approximately equal to that of intramuscular injection once daily Furthermore, its rapidity of action makes the oral administration of cortisone acetate preferable to intramuscular injection in acute conditions requiring immediate high levels of circulating corticosteroid Although the absence of a prolonged effect after cessation of oral therapy materially lessens the hazard of persistent hormonal action in patients with serious signs of steroid overdosage it must be emphasized that this rapid decline in hormonal action may in the presence of effective pituitary adrenal inhibition rapidly project the patient into an acute state of relative adrenal insufficiency The comparatively slow decline of accumulated intramuscular depots of hormone on the other hand tends to prevent this unfortunate sequel of prolonged administration

Cortisone acetate pellets have been employed for the long term substitution therapy of patients with Addison's disease [101] The optimum pellet weight was found to be between 1 0 and 1 5 Gm per implant The average daily dissolution was approximately 10 mg of hormone a day The duration of clinical effectiveness of a single implant averaged four or five months Although the effects of this form of therapy were identical to those observed after cortisone given either intramuscularly or orally, the latter routes of administration are preferable for general clinical use Henderson et al [418] have recently described the use of cortisone acetate pellets in the maintenance treatment of patients with rheumatoid arthritis The pellet implantation is apparently feasible only in patients whose daily hormone requirement is very small

The administration of cortisone intravenously obviously constitutes the method of choice in situations requiring an immediate and sustained high level of circulating corticosteroid The principal therapeutic advantage of this *route lies in the speed with which metabolic effects of maximal intensity* are produced Moreover large quantities of cortisone can be rapidly administered to patients who are unconscious or in whom oral medication is precluded Therefore for acute addisonian crisis or conditions requiring immediate operation intravenous therapy with cortisone is clearly the procedure of choice

Local administration of cortisone acetate has been used extensively only in the treatment of inflammatory eye diseases [416] Topical therapy is economical far less of the hormone being required than in systemic administration In addition, effective steroid concentrations may be achieved without undesirable systemic effects This route has proved effective chiefly in diseases of the anterior segment disorders of the posterior segment are ordinarily treated more effectively by parenteral administration Topical application has been especially helpful in the relief of pain and photophobia associated with corneal lesions Leopold et al [417] have presented evidence of effective penetration of the hormone into intraocular fluids

Two concentrations of ophthalmic suspension are available (0 5 per cent and 2 5 per cent) the choice depending largely upon the severity of the inflammatory reaction to be treated In acute severe disease treatment is often initiated with the more concentrated preparation Maintenance therapy may then be continued with the dilute suspension The most widely employed therapeutic program consists of the administration of 1 or 2 drops of suspension every hour during waking hours and every two hours at night [418] When control of the disease has been established dosage may be reduced to 1 drop every four hours or even four times daily In cases requiring an eye pad the ophthalmic ointment may be more conveniently applied than the suspension The ointment is also useful for nocturnal application Cortisone acetate has been administered subconjunctivally [419] 0 05 to 0 4 cc of the saline suspension being injected under local anesthesia The deposit remains beneath the conjunctiva for several days with a repository effect No contraindications to the topical use of cortisone acetate have been described with the exception of ocular tuberculosis

Cortisone acetate has been administered locally by injection into inflamed joints without therapeutic effects approaching those achieved with hydrocortisone [31] The hormone has been aerosolized for administration by inhalation to patients with bronchial asthma [420] Therapeutic benefit was comparatively slow to appear and aside from the absence of undesirable systemic effects the method appears to offer no real advantage over oral or parenteral administration Cortisone acetate has been applied locally to the skin in patients with chronic discoid lupus erythematosus[421] and other dermatologic disorders with only moderate clinical improvement Again it appears that hydrocortisone is considerably more effective than cortisone after inunction

Hydrocortisone

Hydrocortisone or compound F was first isolated from adrenocortical extracts in 1937 by Reichstein[71] and Mason et al[4,2] Subsequently this compound was shown to be more active than either cortisone or corticosterone in the work performance of adrenalectomized rats[4,3] in the glycogenic test in adrenalectomized rats[1,1] and in its diabetogenic action and antianabolic effect upon protein in force fed normal rats[2,1] In 1948 the isolation of hydrocortisone from the urine of a patient with Cushing s syndrome by Mason and Sprague[4,5] provided direct evidence concerning the chemical nature of a steroid hormone produced by the adrenal cortex This isolation and the discovery in 1949 of the potent anti inflammatory effects of cortisone[10] led to a reawakening of interest in hydrocortisone and in 1950 Hench and his associates[10] reported the beneficial effects of this hormone in rheumatoid arthritis In 1950 the partial chemical synthesis of hydrocortisone was first reported[4,6] Subsequently hydrocortisone has assumed increasing importance with the discovery that it is the principal corticoid in adrenal gland perfusates[4] adrenal venous blood[358,391] and peripheral blood[399] These findings have led to the view that hydrocortisone is the principal hormone secreted by the adrenal cortex

Physiologic Actions

Quantities of hydrocortisone sufficient for general use have only recently become available It is already quite apparent that most of the major metabolic and therapeutic actions of cortisone and hydrocortisone are similar Certain important differences have already been demonstrated however and are pertinent to any comparative evaluation of the two steroids

Early physiologic studies with hydrocortisone administered by intermittent intramuscular or subcutaneous injection demonstrated by various criteria that this hormone possessed greater metabolic activity than cortisone[221,4,3,4,4] That the difference in potency was not due to differences in either the rate of absorption or speed of inactivation has been unequivocally demonstrated by the studies of Ingle and his co workers[427] in which the hormones were administered by continuous intravenous infusion and assayed by the muscle work test Hydrocortisone was found to be approximately twice as effective as cortisone Comparative studies in man in which the intravenous route of administration was used have confirmed the greater potency of hydrocortisone[413] This is demonstrated in Figure 14 which shows the eosinopenic effect of free hydrocortisone to be approximately twice that of cortisone Measurements of other metabolic indexes also reveal a greater activity of hydrocortisone[4,8]

A particularly striking example of the difference in potency between the two hormones is the superiority of hydrocortisone after local administration in the skin[4,9] eye[418] and joints[430] It has been suggested from these findings that cortisone to be therapeutically effective must be transformed to hydrocortisone or that locally applied hydrocortisone is converted more efficiently than cortisone to a hypothetic active metabolite[431] However the

effectiveness of cortisone after local instillation into the conjunctival sac argues against this hypothesis Hollander [31] has suggested that since hydrocortisone is only one-seventh as soluble as cortisone in body fluid it might diffuse less rapidly from the site of local action The final explanation of the difference in local effectiveness between the two hormones is not known

The marked influence observed by Conn et al [432] of the route of administration on the metabolic actions of hydrocortisone acetate has important

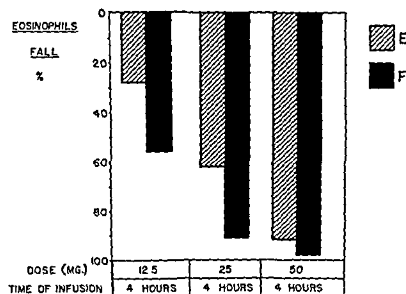


FIG 14 Eosinophil response to the intravenous administration of cortisone (E) and hydrocortisone (F) in a thirty three year old man with Addison s disease Cortisone and hydrocortisone were administered by four hour intravenous infusions Eosinophil counts were performed immediately and at four hours No hormonal therapy other than DCA was administered during these studies

therapeutic implications Hydrocortisone acetate was found to have metabolic effects of the same intensity after oral administration as free hydrocortisone given either orally or by intramuscular injection Intramuscularly administered hydrocortisone acetate however was relatively inert Salassa and his associates [433] attributed this difference to a slow rate of absorption of the acetate ester from the intramuscular depot Boland [434] has confirmed these observations in a study of the antirheumatic effects of hydrocortisone acetate It was believed in addition that the acetate ester was considerably less active than free hydrocortisone when given by mouth

The metabolic effects of hydrocortisone in man have been demonstrated to be qualitatively similar to those of cortisone [90 43 -437] These include a decreased carbohydrate tolerance with glycosuria an increased excretion of total nitrogen and uric acid retention of sodium chloride and water potassium loss, and an increased excretion of calcium and phosphorus

Hydrocortisone acetate has been shown to be capable of correcting the abnormal response of patients with Addison's disease to ingested water loads.[161] Wilkins et al.[81] and Jailer, Louchart, and Cahill[438] have found intramuscularly injected hydrocortisone to be an effective inhibitor of the pituitary adrenal system in patients with the adrenogenital syndrome. Relman and Schwartz[439] demonstrated a depression of I^{131} uptake by the thyroid gland of patients treated with orally administered hydrocortisone acetate. Clark, Blais and Tonning[440] commented on the fact that the administration of hydrocortisone to patients with rheumatoid arthritis in doses capable of giving marked metabolic effects was accompanied by considerably less euphoria than that experienced with equal doses of cortisone. This observation corresponds with the demonstration by Woodbury[146] of a smaller decrease in the electroshock threshold of rats after hydrocortisone acetate. This difference between the two hormones has been employed to good advantage in this clinic in the treatment of patients with Addison's disease in whom average maintenance doses of cortisone induced excessive nervous stimulation. Hydrocortisone has proved effective in the dissolution of lymphoid tissue in patients with a variety of lymphomatous tumors.[148]

An increasing number of reports indicate that hydrocortisone is an effective agent for the suppression of acute inflammatory phenomena[344, 441–445] and of certain hypersensitivity phenomena.[446, 447] It is probable, therefore, that the actions of the hormone on both cellular and humoral mechanisms of defense are also similar to those of cortisone.

In summary, the over-all physiologic actions of hydrocortisone appear to be qualitatively comparable to those of cortisone, although quantitatively its effects are more intense. Whether the differences in local effectiveness of these two hormones reflect a fundamental difference in metabolism remains to be determined. Finally, the state of esterification exerts a greater influence on the rate of absorption and therefore on the intensity of metabolic and therapeutic action of hydrocortisone.

Toxicity

Experience to date has shown that the toxic effects of hydrocortisone are qualitatively similar to those of cortisone. Boland[448] however, has reported that during the maintenance treatment of patients with rheumatoid arthritis fewer adverse effects are observed with free hydrocortisone than with cortisone. He attributes this difference to the fact that smaller doses of hydrocortisone are required to control the disease. A greater antirheumatic activity of free hydrocortisone does not appear to be accompanied by a corresponding increase in tendency to produce toxic complications.

Absorption, Intermediary Metabolism and Excretion

Absorption. Numerous observations that the oral administration of hydrocortisone as either the acetate or the free alcohol leads to striking alterations in carbohydrate, protein and electrolyte metabolism indicate that the hormone is effectively absorbed from the gastrointestinal tract

This is further illustrated by the studies of Nelson et al [383] on the levels of plasma 17 hydroxycorticosteroids after oral administration. These workers reported that the oral administration of hydrocortisone, as either the acetate or the free alcohol led to a prompt rise in plasma 17 hydroxycorticosteroids with a peak at approximately one hour and a gradual return to control levels in four to eight hours. On the other hand when hydrocortisone acetate was administered intramuscularly as a suspension in physiologic saline solution only slight metabolic effects were observed and no appreciable rise in the level of plasma 17 hydroxycorticosteroids occurred.

Intermediary Metabolism There is strong evidence that hydrocortisone is the principal hormone secreted by the adrenal cortex. This compound has been shown to be the chief corticoid in dialysates of the peripheral blood of dogs [389] in the adrenal venous blood of dogs which have been given corticotropin [358,391] and in the perfusates of bovine adrenal glands [4]. Moreover the addition of corticotropin to the perfusing fluid of bovine adrenal glands increases the output of hydrocortisone from the isolated gland.

The biosynthesis of hydrocortisone from acetate has been demonstrated in hog adrenal slices incubated with C^{14} acetate[395] and in beef adrenal glands through which radioactive acetate has been perfused [4]. Cholesterol however was found to be considerably more effective than acetate as a precursor [4]. From analysis of the isotopic data it was reasoned that synthesis of hydrocortisone from acetate and from cholesterol may proceed along separate pathways. Some inkling of the intermediate steps involved has come from the finding that the perfusion of progesterone through beef adrenal glands leads to an increased formation of hydrocortisone and the observation that compound S may serve as a precursor for hydrocortisone in the isolated adrenal gland[4] and in adrenal homogenates [443].

Schneider and Horstmann[398] have presented evidence that hydrocortisone like cortisone is rapidly metabolized in the liver. Incubation of the hormone with rat liver slices and examination of the reaction products with the aid of ultraviolet spectrophotometry paper chromatography and the Porter Silber and periodate oxidation assays indicated that rapid reduction of the α β unsaturated ketonic grouping in ring A and extensive degradation of the side chain at C-17 occurred. Similar findings were obtained when hydrocortisone was perfused through the isolated rat liver [395].

Excretion The administration of hydrocortisone to patients with adrenal insufficiency like that of cortisone leads to an increase in the urine of 17-ketosteroids and steroids with an α ketol side chain at C 17. Similar findings are observed in subjects with intact adrenal glands provided the dose of hydrocortisone is sufficiently high with small doses a fall in urinary 17 ketosteroid levels may occur. As with cortisone the administration of hydrocortisone to patients who have undergone bilateral orchiectomy and bilateral complete adrenalectomy for metastatic carcinoma of the prostate has been found to lead to a rise in urinary biologic androgen excretion [409]. In these patients hydrocortisone has been observed to be a more effective precursor of both 17-ketosteroids (Figure 15) and androgens than cortisone although

even at a dose of 300 mg a day the level of urinary androgens does not exceed that of a normal man

Hydrocortisone has been isolated from normal urine[347 410] and from the urine of patients with Addison's disease[411 41] and normal human subjects who have been given cortisone[408] These findings and the recent observation that the administration of hydrocortisone to human subjects led to an increased excretion of cortisone in the urine[450] provide strong evidence that the reversible reaction hydrocortisone ⇆ cortisone may occur *in vivo* Although no detailed investigations of specific steroids in the urine of human subjects who have received hydrocortisone have been reported it may be inferred from studies of the steroids of normal urine and from studies of degradation

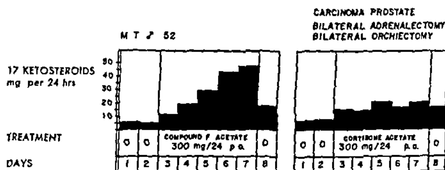


Fig 15 Effect of hydrocortisone acetate and cortisone acetate upon the 17 keto steroid excretion after bilateral adrenalectomy and bilateral orchiectomy in a fifty two year old man with carcinoma of the prostate

in vitro[1 8] that the metabolism of hydrocortisone is similar to that of cortisone The hormone may be excreted unchanged reduction of the $\alpha\beta$ unsaturated ketone grouping in ring A may occur with the formation of tetrahydrocortisone and the tetrahydro hydrocortisone, and finally there may be degradation of the side chain at C-17 with the production of 11 oxy 17 ketosteroids

Preparations and Routes of Administration

Five preparations of hydrocortisone are currently available tablets for oral administration containing 5 10 or 20 mg of free hydrocortisone for intra articular or intrabursal injections a microcrystalline suspension of hydrocortisone acetate in physiologic saline solution containing 25 mg per cc (0 9 per cent benzyl alcohol as a preservative and small quantities of polyoxyethylene sorbitan mono oleate and sodium carboxymethylcellulose as suspending agents are also present) a microcrystalline suspension of hydrocortisone acetate in a solution of phosphate buffer for ophthalmic use containing 5 or 25 mg per cc with suitable preservative ophthalmic ointment of 1 5 per cent concentration of hydrocortisone acetate in petrolatum base and topical ointment with 1 per cent and 2 5 per cent concentration of hydrocortisone acetate

Orally administered hydrocortisone is adequately absorbed from the gastrointestinal tract The time response curve of the oral preparation is

quite comparable to that of cortisone acetate and in fact approaches that obtained by a single intravenous injection of hydrocortisone

The saline suspension of hydrocortisone acetate is specifically dispensed for intra articular injection in the treatment of localized noninfectious inflammatory joint disease The indications for its use in rheumatoid arthritis and the proper technic of injection have been well outlined by Hollander [31] and by Boland [434] Dosages range between 10 and 50 mg depending upon the size of the joint and the severity of the inflammatory process The duration of clinical improvement after injection is variable but ordinarily it lasts for 3 to 21 days That the beneficial effects produced by hydrocortisone after local injection are nonspecific is indicated by its effectiveness in osteoarthritis traumatic arthritis gouty arthritis acute bursitis and the acute pleuritis of lupus erythematosus [31]

The local administration of hydrocortisone acetate has also proved effective in disorders of the anterior segment of the eye[451] and in certain inflammatory lesions of the skin [4 9] The usual dosage schedule consists of 1 or 2 drops of the ophthalmic suspension at hourly intervals during the day and every two to four hours at night Experience to date indicates that hydrocortisone is somewhat more effective than cortisone in the treatment of ocular inflammatory disease [418] Goldman[45] has demonstrated in several ingenious experiments a much greater suppression of cutaneous inflammation by intracutaneously injected hydrocortisone than by cortisone Subsequently Sulzberger and Witten [452] using an ointment containing 25 mg of hydrocortisone acetate per Gm of base consisting of lanolin and petrolatum observed definite improvement in the lesions of some patients with atopic dermatitis although no response was obtained in cases of chronic discoid lupus erythematosus or chronic lichenoid dermatoses

Administration of the saline suspension of hydrocortisone acetate by intramuscular injection is not recommended for therapeutic use because of its slow absorption rate which results in a considerable reduction in metabolic and therapeutic activity

Solutions of hydrocortisone for intravenous use have been prepared in this laboratory[413] in the following manner a sterile suspension of free hydrocortisone (*free alcohol*) in physiologic saline solution containing 25 mg per cc is added to sterile 95 per cent ethyl alcohol and sterile water in the order given in the proportions of 4 cc of steroid suspension 5 cc of alcohol and 3 cc of water The resulting clear solution is immediately diluted as desired in physiologic saline or dextrose solution for intravenous administration When concentrations of hydrocortisone not exceeding 20 mg per 100 cc are required the saline suspension of hydrocortisone may be dissolved directly in either the saline or the dextrose diluent The majority of metabolic and therapeutic studies on the intravenous administration of adrenocortical hormones have employed hydrocortisone and a satisfactory preparation will soon be available for clinical use

In situations in which a rapid and intense hormonal effect is necessary the intravenous infusion of hydrocortisone is the procedure of choice since

the chief advantage offered by this route is the rapidity with which metabolic effects of *maximal* intensity are produced Figure 16 shows the changes elicited in a fasting normal subject by the intravenous administration of hydrocortisone at a rate of 12 mg per hour A satisfactory eosinopenia and uricosuria were obtained Particularly striking were the rapid and impressive

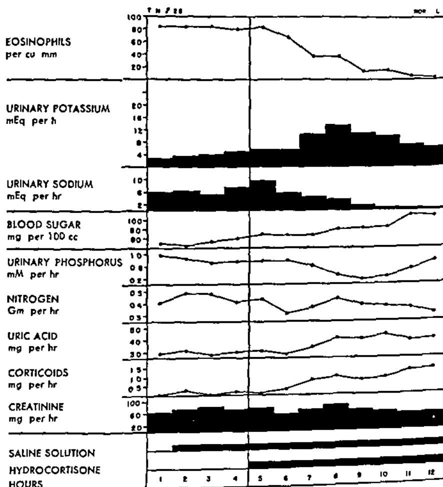


Fig 16 Changes obtained in a normal subject with the intravenous administration of hydrocortisone (12 mg per hr) The subject was in the fasting state throughout the experiment All urinary analyses were performed on specimens collected hourly (Saline solution was infused at a rate of 60 cc per hour)

changes in urinary electrolyte excretion a pronounced rise in potassium output and an almost complete suppression of sodium excretion The absence of an increase in total urinary nitrogen indicates that during the initial acute phase of hormonal action the elevation of blood sugar cannot be adequately accounted for by an augmented gluconeogenesis from protein The progressive rise in total 17 hydroxycorticoid excretion establishes the time-response curve of urinary corticoid excretion in the presence of a sustained high level of circulating hydrocortisone In view of the intensity of

hormonal effects upon both organic and inorganic metabolism intravenous hydrocortisone therapy is clearly indicated in existing or potential states of acute adrenocortical insufficiency

In summary if the pharmacologic triad of increased potency without proportionate increase in toxicity and increased effectiveness when administered locally in the joint and the eye are borne out by future clinical experience, it appears possible that hydrocortisone will become the adrenal corticoid of choice in the therapy of diseases in which 11 17 oxysteroids are of value

Adrenocortical Extracts

Two types of adrenocortical extracts are available commercially for clinical use extracts derived from beef adrenal glands in aqueous solution suitable for subcutaneous intramuscular or intravenous use, and a single, highly purified extract derived from hog adrenal glands prepared in sesame oil for intramuscular use only and assayed in terms of its corticosterone and cortisone equivalence

For the daily maintenance therapy of patients with Addison s disease adrenal extracts have been replaced almost entirely by a combination of DCA and cortisone or hydrocortisone Aqueous adrenal extract has a useful place in the therapeutic armamentarium of acute adrenal crisis particularly in the absence of a commercially available preparation of cortisone or hydrocortisone for intravenous use In the treatment of adrenal crisis or acute adrenal insufficiency adrenocortical extracts may be used as follows 30 to 50 cc of aqueous adrenal extract injected rapidly as an intravenous infusion followed by 10 cc of aqueous adrenal extract or 2 cc of lipoadrenal extract intramuscularly every one or two hours for twelve hours and then every two to three hours for the next twelve hour period this is followed by 5 to 10 cc of aqueous adrenal extract or 1 to 2 cc of lipoadrenal extract Subsequently the dose is maintained but the period of administration is increased to intervals of three four and six hours [48]

Whether or not adrenal extracts possess any distinct value in the maintenance therapy of Addison s disease over and above that of cortisone and hydrocortisone supplemented with DOC is not known Certainly the over all difference cannot be great since cortisone and hydrocortisone have been used repeatedly with great success as the sole source of adrenal hormone therapy in the treatment of adrenal crisis

Corticotropin

The classic studies of Smith[454 455] showed that marked atrophy of the adrenal cortex followed hypophysectomy in the rat and that this change could be prevented by intramuscular implantation of rat pituitary glands Sub equently in 1933 four groups of investigators[456-459] reported that anterior pituitary extracts could produce adrenocortical hypertrophy in animals Since that time there has been steady progre s in the preparation of highly potent pituitary fractions possessing tropic' activity with respect to the adrenal cortex

Nature of Corticotropin

The adrenocorticotropic activity of pituitary extracts has been assayed principally by three methods the first being that based on adrenal size and structure Collip et al [459] originally determined the effects of pituitary extracts upon adrenocortical size and histologic structure in hypophysectomized rats Subsequently various modifications of this procedure have been introduced [460–46] The second type is the Sayers procedure The observation by Sayers et al [463] that the ascorbic acid content of the adrenal gland of the rat is rapidly reduced by a single dose of corticotropin led to the development of a sensitive assay method for corticotropin in hypophysectomized rats [464] Modifications designed to simplify this method when applied to a large number of animals have been introduced by Munson Barry and Koch [465] The third method which is applied to human subjects assays the adrenocorticotropic activity of pituitary preparations by the change in circulating eosinophils [48 466 467 481 48] after intramuscular administration of the hormone and by the change in blood eosinophils and urinary steroids[7 468] after intravenous infusion of corticotropin Although assay methods based on changes in adrenal weight and on ascorbic depletion have been essential in facilitating the purification of corticotropin the most reliable method of predicting the therapeutic efficacy of a given preparation has been the determination of its activity in man when it is administered by the route to be employed in clinical therapy

After development of the Sayers assay the first standard of potency the preparation La 1 A [469] was established and potency was thereafter expressed in terms of this preparation on a weight basis Subsequently La 1 A was set up as an international standard and the activity of 1 mg was defined as 1 international unit Recently because of the short supply of the international standard a new standard has been established by the *United States Pharmacopoeia* whereby by definition 1 U S P unit equals 1 international unit

The history of the development of extraction and purification procedures for the preparation of corticotropin has been ably reviewed by Astwood et al [470] The first systematic study of methods for the isolation of corticotropin was carried out by Collip and his associates[471–473] between 1933 and 1941 In 1942 and 1943 almost simultaneous reports by Li et al [474 475] and Sayers and his co workers[476 477] announced the isolation of corticotropin in pure form Modifications of the acetone–hydrochloric acid method of Lyons[478] were used and purification was carried out by salting out and isoelectric precipitation In both instances the product was regarded as a pure protein on the basis of electrophoretic and ultracentrifuge studies and its relative freedom from other pituitary hormones The molecular weight was estimated to be 20 000 and the isoelectric point 4 7 Subsequent investigations however have shown that adrenocorticotropic activity may be separated from this protein by a number of methods In 1943 Tyslowitz[479] established the fact that ultrafiltrates of aqueous and glacial acetic extracts of porcine pituitary powder possessed corticotropic activity Recently the method

of ultrafiltration has been shown to be an efficient means of purifying corticotropin [480]

The finding that the purified protein preparation of Li et al and Sayers et al could be subjected to partial degradation by pepsin[475] or by boiling in one tenth normal solution of hydrochloric acid without loss of activity led Li[481] to suggest that the activity of the purified protein rested in a constituent peptide fragment that could be split off by these hydrolytic procedures The average size of the constituents of the hydrolysates corresponded to peptides with 7 to 9 amino acid residues [48] Recently with the aid of chromatographic fractionation Li et al [483] obtained active fractions with mean molecular weights varying between 410 and 2 800 an indication that corticotropic activity may be possessed by a series of peptides of differing composition Lesh and his associates [484] using peptic digestion obtained fractions 100 to 150 times more active than the original protein with molecular weights estimated to be between 2 500 and 10 000

The most recent advance in the purification of corticotropin has been the use of oxycellulose to adsorb the hormone from glacial acetic acid extracts of pituitary tissue [485] By this means highly potent corticotropin preparations assaying up to 100 units per mg have been obtained On the basis of these and other studies Astwood et al [470] have concluded that whereas corticotropin has yet to be isolated in pure form one can be reasonably sure that the hormone is a water soluble nonvolatile organic compound of modest molecular size It is colorless has no unique ultraviolet absorption spectrum above 240 millimicrons and contains no large lipid component and no carbohydrate sulfur phosphorus or heavy metal The fact that the biologic activity is destroyed by trypsin pepsin and carboxypeptidase suggests that one or more peptide bonds are present The finding that there is a loss of potency upon treatment with nitrous acid or dinitrofluorobenzene indicates that one or more amino groups are essential components of the molecule Inactivation on esterification suggests that one or more carboxyl groups are likewise essential for biologic activity Finally the behavior of corticotropin preparations in the presence of organic acids and cation exchange resins indicates that the hormone may possess a strongly basic group

Release of Corticotropin

It is well established that the release of corticotropin from the anterior pituitary gland is an essential element in the mechanism responsible for adrenocortical activation In man highly purified preparations of corticotropin have been observed to produce all the changes elicited by the administration of crystalline adrenal steroids In animals exogenous stress increases adrenocortical weight and decreases the concentration of cholesterol ascorbic acid and sudanophilic material In the absence of the pituitary gland none of these changes is observed Furthermore hypophysectomy results in adrenocortical atrophy [455] and the hypophysectomized animal like the adrenalectomized animal is extremely sensitive to a great variety of non specific stresses [456 457]

Source of Corticotropin There is little agreement concerning the specific cellular source of corticotropin in the anterior pituitary gland Early evidence derived from the study of the hypophysis in patients with Addison s disease suggested that the basophils were the site of secretion [488] The correlation described by Cushing[489] between the presence of a basophilic pituitary tumor and the existence of clinical manifestations now recognized to be the consequence of adrenocortical hyperfunction has also implicated the basophilic cells as the source of corticotropin D'Angelo et al [490] noted that starvation in animals was characterized by a decrease in the number of pituitary acidophils an increase in the number of basophils and adrenal hyperplasia These findings were interpreted as indicating an increased output of corticotropin from the basophils but the possibility remains that hormones other than corticotropin were primarily involved Finerty and Briseno-Castrejon[491] observed that in unilaterally adrenalectomized rats with compensatory hypertrophy of the remaining adrenal gland the number of acidophils in the anterior pituitary gland was considerably increased They therefore postulated that corticotropin was derived from the acidophilic cells Pearse[49] concluded that histochemical technics are inadequate at the present time to identify the source of corticotropin Recently Marshall[493] prepared fluorescein tagged antiserums to hog corticotropin Examination under fluorescent light of hog pituitary slices exposed to the tagged antiserums showed that only the basophils stained to any significant degree suggesting that that cell is the source of corticotropin Although the question cannot be considered settled conclusively majority opinion favors the origin of corticotropin from the basophils

Regulation of Secretion An increase in the rate of corticotropin release has been assumed to be the mechanism responsible for the increase in adrenocortical secretion observed in a wide variety of situations Three types of regulatory mechanisms have been considered to control the rate of discharge of corticotropin humoral sympathicoadrenal and neurohumoral

Humoral Control Sayers[193] has suggested that the regulation of the adrenocortical secretion of steroids and the pituitary release of corticotropin are controlled by the blood level of adrenocortical hormones Thus a fall in the circulating level of adrenocortical steroids as a result of increased cellular utilization serves as a stimulus to augment the secretion of corticotropin Conversely an abnormally high blood level of corticosteroids inhibits the rate of corticotropin release A considerable body of direct evidence for this hypothesis has been accumulated in both animals and man The adrenocortical hypertrophy that follows unilateral adrenalectomy appears to represent a compensatory increase in corticotropin output as a result of a temporary decrease in the circulating level of adrenocorticosteroids The prolonged administration of adrenal steroids results in adrenocortical atrophy [9 494] Furthermore the discharge of corticotropin in response to exogenous stress may be blocked by the administration of cortical hormones and the amount of steroid required to suppress corticotropic activity varies directly with the intensity of the stress [19] The e relations have been considered to demon

strate that the rate of corticotropin release from the pituitary gland reflects the varying requirement of the organism for adrenocortical hormones Sayers and Sayers[194] have suggested that the regulating effect of circulating cortical steroids upon corticotropin discharge involves a direct effect of the steroids upon the hypophysis

The main obstacle to accepting a mechanism based on reciprocal blood levels of adrenal steroids and corticotropin as the sole regulator of corticotropin release concerns the rapidity with which the pituitary adrenal system is capable of responding to certain stimuli For example Cray and Munson[495] have shown that after intravenous histamine injection in rats corticotropin is discharged within a few seconds Long[496] has described an equally rapid response to sensory nerve stimulation Nevertheless it appears that the peripheral humoral mechanism of pituitary adrenal control contributes to the basic regulation of the release of corticotropin

Sympathicoadrenal Control As an extension of the classic view of Cannon[497] concerning the ubiquitous role of the autonomic nervous system and epinephrine in the preservation of homeostasis Long et al [498,499] have postulated that the prompt release of corticotropin from the hypophysis under conditions of stress is a result of the secretion of epinephrine In support of this concept they have reported a delay in the adrenocortical response to stress in the demedullated animal and have demonstrated that the direct application of epinephrine to pituitary transplants in the anterior chamber of the eye results in a significant degree of eosinopenia [510] Previous studies had demonstrated a satisfactory correlation between eosinopenia and adrenal ascorbic acid depletion after epinephrine Considerable disagreement exists however concerning the capacity of the demedullated or sympathectomized demedullated animal to respond to stress most workers[501–503] have reported normal adrenocortical responses in these animals Vogt[504] found that the intravenous infusion of epinephrine in splanchnicectomized dogs resulted in a prompt rise in the adrenal venous content of substances capable of protecting adrenalectomized animals from cold stress The effect was attributed[505] to an increase in the rate of corticotropin release However the specific circumstances under which this response was obtained (splanchnicectomized dogs) should be considered carefully in application of these observations to the intact organism and to other species

Recent studies in *man* have failed to support the concept of epinephrine as a physiologic activator of the pituitary adrenal system Although it is well known that the administration of adequate doses of epinephrine to human subjects produces a significant degree of eosinopenia [50] subsequent investigations have not succeeded in demonstrating that this fall in the number of circulating eosinophils is the result of an increase in the rate of secretion of steroid hormones from the adrenal cortex After administration of epinephrine an eosinopenia can be elicited in patients with Addison s disease[50] and has frequently been observed to follow complete bilateral adrenalectomy [3] The administration of epinephrine has resulted in a marked fall in circulating eosinophils even though repeated intravenous infusions of corticotropin have

produced no effect Nelson[506] recently found that the blood level of 17 hydroxycorticosteroids in normal subjects and patients did not change after the intravenous injection of epinephrine despite a fall in blood eosinophils Jeffries[507] was also unable to produce either metabolic changes or urinary steroid changes with epinephrine consistent with increased corticotropin release Thorn et al [3] compared the effects of intravenous subcutaneous and intramuscular injections of epinephrine in normal subjects with those produced by corticotropin Despite the occurrence of eosinopenia no rise in the

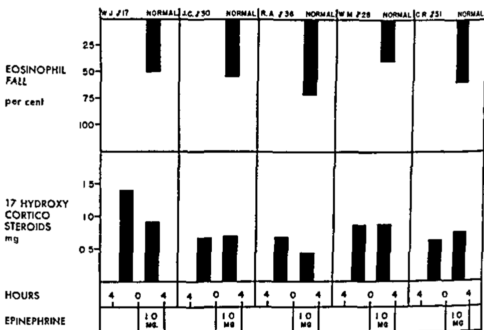


FIG 17 Eosinophil and 17 hydroxycorticosteroid responses to intravenous infusion of epinephrine 17 Hydroxycorticosteroids were measured on four hour urine samples collected before and during epinephrine administration Eosinophils were counted at the beginning and completion of epinephrine infusion (From Thorn Jenkins and Laidlaw [3])

urinary output of 17 hydroxycorticosteroids was obtained (Figure 17) Although the administration of extremely large quantities of epinephrine (such as 15 to 30 mg per day) to patients receiving a sympatholytic agent has been demonstrated to result in an increase in urinary 17 ketosteroids [508] the doses of epinephrine required to produce this effect can hardly be considered physiologic

It must be concluded that with the methods at present available it has not been possible to demonstrate an elevation in the rate of adrenocortical steroid secretion in *man* with reasonable doses of epinephrine furthermore, epinephrine has been shown to produce eosinopenia in the absence of functioning adrenocortical tissue Although the fall in circulating eosinophils that occurs after corticotropin administration has been found to be closely correlated with the rise in urinary 17 hydroxycorticosteroids [3] it is evident

that eosinopenia alone does not provide a reliable index of adrenocortical activation after either the administration of epinephrine or exposure of the patient to environmental conditions capable of stimulating the release of epinephrine or other eosinopenic agents

Neurohumoral Control There is a growing body of evidence that the secretory functions of the anterior pituitary gland are significantly influenced by the hypothalamus In view of the established importance of hypothalamic centers in the regulation of the activities of the autonomic nervous system it is evident that the hypothalamus occupies a strategic position for the integration of the adaptive and regulatory functions of the endocrine and vegetative nervous systems Definitive evidence for the stimulation of corticotropin discharge by the hypothalamus has been derived from the experiments of Harris[509,510] and Hume[510,511] These investigators have shown that strategically placed lesions in the hypothalamus of both rabbits and dogs can abolish the pituitary adrenal response to exogenous stress and conversely by utilizing remote control stimulation of implanted coils as described by Harris[51] that electric stimulation of carefully localized areas of hypothalamus produces a lymphopenia and eosinopenia interpreted as indicating adrenocortical stimulation consequent to the discharge of corticotropin from the anterior pituitary gland Stimulation of the gland itself was quite ineffective in eliciting an adrenocortical response

Results obtained by various workers on the effect of stalk section upon anterior pituitary function have been highly variable The work of Popa and Fielding[513] in 1930 demonstrated that the collection of blood vessels that courses along the pituitary stalk is actually a portal system Subsequently Wislocki[514] and others[515,516] established the direction of flow in this portal system as being from the capillary plexus of the median eminence to the sinusoids of the pars distalis The careful work of Harris[512] has demonstrated the importance of this vascular bed to the normal function of the anterior pituitary gland It now appears that pituitary stalk section may interfere with the secretory function of the pars distalis provided regeneration of the portal system is successfully prevented Confirmatory evidence for this has been derived by Harris and Jacobsohn[517] from the study of functional hypophyseal grafts Hypophyseal tissue was grafted into hypophysectomized rats in two locations beneath the temporal lobe of the brain and beneath the median eminence of the tuber cinereum Adequate revascularization of the latter grafts from the hypophyseal portal system was demonstrated Histologic study showed that grafts beneath the temporal lobe exhibited an abnormal chromophobe to chromophil cellular ratio despite apparently normal vascularization whereas grafts beneath the median eminence presented a normal pattern of cellular differentiation Animals possessing subtemporal grafts showed a definite lack of gonadotropic and growth hormone activity and the adrenal glands in these animals were moderately atrophic In contrast animals with grafts beneath the median eminence exhibited normal reproductive function and histologic examination of the ovaries and adrenal and thyroid glands revealed a normal structure However Cheng et al [518]

and Fortier[519] have shown that hypophyseal transplants in the anterior chamber of the eye are capable of discharging corticotropin in response to acute stress despite abnormalities of cellular differentiation in the transplanted tissue The former utilized reduction in adrenal ascorbic acid content as an indication of corticotropin release whereas the latter employed the eosinophil response

On the basis of the evidence cited above, it may be postulated that the release of corticotropin by the anterior pituitary gland is subject to hypothalamic control through a humoral mechanism mediated directly through the hypophyseal portal vascular bed and indirectly especially during conditions of stress through the systemic circulation It is to be emphasized however that the ultimate proof of such a mechanism awaits the actual demonstration of an increase in the circulating level of corticotropin

Physiologic Actions

The physiologic actions of corticotropin may be discussed conveniently under two headings the influence of this hormone on the adrenal cortex which is considered in detail in the preceding chapter and its effects upon the organism In the following sections clinical studies of the effects of corticotropin upon the adrenal cortex and upon the organism will receive particular attention

Adrenal Cortex *Morphology* Landing and Ferozi[520] studying the morphology of the adrenal glands of 9 children with acute leukemia and 1 child with the nephrotic syndrome who died during corticotropin therapy found that in the former the weight of the adrenal glands was above normal, the cells of the fascicular and reticular zones were larger than normal and their fat content was decreased The zona glomerulosa showed no apparent change In the patient with nephrosis however there was an increase in zone thickness and cell size with a decrease in fat in all three zones of the adrenal cortex

It thus appears that in man although the morphologic response of the zona glomerulosa to corticotropin may be slight when compared to that of the fascicular and reticular zones the entire adrenal cortex is sensitive to corticotropin stimulation This is apparently true also in both the mouse[521] and the dog[522] In the rat however the zona glomerulosa seems to be relatively independent of pituitary control as indicated by its failure to show involutionary changes after hypophysectomy[523] or administration of cortisone[191, 509] and by its failure to reveal proliferatory or secretory changes after the administration of corticotropin[193]

Chemistry ASCORBIC ACID Investigations of the changes in adrenal ascorbic acid under a variety of experimental conditions have been ably reviewed by Sayers and Sayers[193] In general increased adrenocortical activity is associated with a reduction in the concentration of adrenal ascorbic acid Administration of corticotropin leads to a rapid depletion of adrenal ascorbic acid in the guinea pig and the rat[524] In rats the concentration of ascorbic acid falls appreciably within 20 minutes of injection of the hormone decrease

being maximal at 1 hour but within 3 hours the concentration has begun to rise and in 9 to 12 hours has returned to normal With repeated administration of corticotropin the adrenal ascorbic acid remains at a low level but this is only temporary for with prolonged stimulation by the "tropic" hormone the concentration of ascorbic acid in the adrenal cortex gradually returns to normal

The part played by ascorbic acid in the metabolic processes of the adrenal cortex is unknown Patients with scurvy excrete corticoids at a normal rate[5 5] Finally corticotropin produces a normal fall in adrenal cholesterol content together with a lymphopenia in guinea pigs in which a scorbutic diet has virtually eliminated the concentration of ascorbic acid in the adrenal gland[5 6]

Little is known of the effect of corticotropin upon the content of ascorbic acid in the human adrenal cortex Beck et al[527] observed an initial rise in blood and urinary ascorbic acid in patients receiving corticotropin With continuing stimulation however the elevated blood and urinary levels returned to normal These authors suggested that their findings indicated a rapid release and synthesis of ascorbic acid by the adrenal cortex in response to corticotropin

CHOLESTEROL Cholesterol is present in high concentration in the adrenal cortex Its relation to the secretory activity of the adrenal cortex has been reviewed by Sayers et al[463] as well as in the preceding chapter

α KETOLIC CORTICOIDS It is well known that the administration of corticotropin to man is followed by an increased excretion of α ketolic corticoids (formaldehydogenic steroids or reducing corticosteroids) in the urine (Figure 12) These consist largely of tetrahydrocortisone tetrahydrohydrocortisone hydrocortisone and cortisone[408] That these urinary changes reflect an increased synthesis as well as an increased secretion of α ketolic corticoids from the adrenal gland is evident from studies with the isolated adrenal gland[4] and adrenal slices[525] Hechter and his co-workers[4] showed that when corticotropin was added to blood that was being perfused through bovine adrenal glands the resulting increase in α ketols in the perfusate could not be explained by the small decrease in the corticoid content of the gland Furthermore Haynes et al[525] observed that corticotropin enhanced the incorporation of C^{14} from radioactive acetate into hydrocortisone in the presence of beef adrenal slices Further details of these and other steroids formed under the influence of corticotropin have been presented in the preceding chapter

17 KETOSTEROIDS It is well known that the administration of cortico tropin to man leads to an increased excretion of 17 ketosteroids in the urine Dobriner and his co workers[408 529] have shown that there is an increase both in 17 ketosteroids with an oxygen atom at C-11 e g 11 hydroxyandrosterone 11 hydroxyetiocholanolone and 11 ketoetiocholanolone and in those lacking an oxygen atom at C 11 such as androsterone and etio cholanolone The administration of cortisone to man on the other hand results in an increa e only in 11 oxy 17 ketosteroids It is believed that the

adrenal precursors of the 11-desoxy-17-ketosteroids may be hormones that, unlike cortisone, hydrocortisone and corticosterone, do not possess an oxygen atom at C 11, e.g., 11-desoxy-17-hydroxycorticosterone (compound S) and 17-hydroxyprogesterone. This belief is supported by the demonstration that the administration of such substances labeled with radioactive carbon leads to the excretion in the urine of radioactive androsterone and etiocholanolone.[424] Furthermore, the administration of large doses (300 mg. per day) of hydrocortisone, cortisone and corticosterone to patients who had undergone orchiectomy and bilateral adrenalectomy for metastatic carcinoma of the prostate did not raise the level of biologically active urinary androgens above that of a castrated male.[409] Finally, it is of interest that Gassner et al.[530] have reported the isolation of a fraction that possessed androgenic activity and gave the reaction for 17-ketosteroids from the adrenal venous blood of cows that had been given corticotropin. These findings make it seem improbable that hydrocortisone is the sole steroid secreted by the adrenal cortex, as proposed by Conn et al.[437]

The 17-ketosteroid dehydroisoandrosterone has long been considered to be of adrenal origin. This is based on its isolation from the urine of castrate men[531] and from the urine of normal[532] and castrate women.[533] It has been found in large amounts in the urine of patients with adrenal tumors.[534] Furthermore, it has not been demonstrated to be a metabolite of testosterone.[535] Recently, Landau et al.[525] and Wolfson and his associates[78] have observed increases in the Pettenkofer chromogen in the ketonic fraction of the urine of patients receiving corticotropin. Under similar circumstances Ronzoni[536] has reported an increase in the color given by the Allen reaction.[537] Although these reactions are given by dehydroisoandrosterone, doubts about their specificity for dehydroisoandrosterone alone[538, 539] make it uncertain at present whether corticotropin induces the adrenal cortex to secrete this steroid or its precursor.

ESTROGENS. In 1939 Beall[540] reported the isolation of estrone from ox adrenal glands. Excessive quantities of estrogens, as determined by bioassay, have been detected in the urine of certain patients with adrenal tumors.[541, 542] From the urine of 1 such subject, Mason and Kepler[543] were able to isolate estrone. After corticotropin administration, Nathanson et al.[544] observed rises in urinary estrone, estradiol and estriol in 3 female patients but not in 2 male subjects studied. One of the female patients was subsequently found to have atrophic ovaries, and it was believed that the origin of the estrogens must have been the adrenal cortex. Paschkis,[545] using a bioassay method, noted rises in estrogen excretion in the urine of 2 male patients after corticotropin stimulation. These observations suggest that estrogens or estrogen precursors may be liberated by the adrenal cortex in response to corticotropin.

PROGESTERONE. Progesterone was first isolated from ox adrenal glands in 1938 by Beall and Reichstein.[546] Its urinary excretory product, pregnanediol, has been found in increased amounts after the intramuscular administration of DOC to man.[40] Dobriner et al.[475] have noted an increased excretion of pregnanolone, a probable reduction product of progesterone, in

the urine of patients after corticotropin stimulation but not after the administration of cortisone Recently an increased excretion of pregnanediol like substances has been observed in man after major surgical procedures and the administration of corticotropin but not of cortisone [547] It seems probable from these observations that progesterone or a precursor of this compound is released by the adrenal cortex in response to corticotropin

In summary it appears that corticotropin stimulates the synthesis as well as the release of steroids from the adrenal cortex Hydrocortisone and corticosterone are the major corticoids liberated It seems however that electrolyte regulating compounds more highly potent than these substances are released in response to corticotropin In addition there is strong evidence that androgens or androgen precursors other than hydrocortisone or corticosterone are produced by the adrenal cortex Finally there is evidence that estrogens and progesterone or precursors of these compounds may be secreted by the adrenal gland after corticotropin stimulation

The Organism *Effects Mediated by the Adrenal Cortex* In general, except in cases in which the adrenal cortex is unable to respond or corticotropin 'resistance' has developed the biologic effects of corticotropin are qualitatively similar to those of cortisone and hydrocortisone The actions of cortisone and hydrocortisone have been presented in some detail Only the effects of corticotropin that differ appreciably from those of the two corticoids are discussed

In short term experiments (six to nine days) in man Conn et al [548] and Perera and his associates[549] observed that cortisone had little or no effect upon the level of serum cholesterol With prolonged cortisone administration however Adlersberg Schaefer and Drachman[55] noted that the total serum cholesterol frequently increased with a concomitant rise in cholesterol esters In contrast in short term studies with corticotropin there was a precipitous fall in total serum cholesterol on the third to the fifth day after the institution of therapy this decrease was mainly at the expense of the ester fraction [548] In addisonian patients no change in the concentration of serum cholesterol followed corticotropin administration Conn et al [548] postulated that the serum cholesterol particularly the ester fraction might serve as a precursor in the synthesis of adrenocortical hormones after the adrenal cortex has been depleted of its reserve supply of cholesterol during stimulation by corticotropin With prolonged administration of corticotropin however Adlersberg Schaefer and Drachman[550] observed a gradual rise in serum cholesterol concentration that was largely due to an increase in the concentration of cholesterol esters Wolfson and his associates [01] suggested that the elevation in serum cholesterol seen with both cortisone and corticotropin therapy was in part a manifestation of a depression of thyroid function

A major but as yet unsolved problem is the interpretation in terms of the corticoids responsible of the pronounced sodium and chloride retention that follows corticotropin administration Although the exact status of DOC as a natural mineralocorticoid is still uncertain the recent isolation of a highly potent electrolyte regulating compound from the adrenal venous

blood of animals[5] suggests that corticotropin might stimulate the adrenal cortex to release a specific salt retaining substance in addition to the glucocorticoids On the other hand whereas it was originally thought that the secretion of cortisone and hydrocortisone alone from the adrenal cortex could not account for the degree of sodium and chloride retention observed after the administration of corticotropin recent studies[1] have shown that the intravenous infusion of cortisone or hydrocortisone at a rate of 12 mg per hour can result in the virtual extinction of sodium from the urine of human subjects Thus the salt retention that follows corticotropin administration can conceivably be explained on the basis of an increased secretion of cortisone or hydrocortisone Finally it is possible that corticoids such as corticosterone (compound B) and dehydrocorticosterone (compound A) which are known to be more potent in electrolyte regulation than the 11 17 oxysteroid contribute to a considerable degree to the over all effect of sodium and chloride retention of corticotropin

Changes in the anterior pituitary gland have been observed in patients receiving long continued corticotropin treatment An increase in the number of basophils with the development of Crooke s changes and basophilic stippling of many of the chromophobe cells were observed by Colden et al[531] in the anterior pituitary glands of 2 patients Similar findings were obtained by Laqueur[65] Landing and Feriozi[570] described an increase in size and degranulation of the pituitary basophils of leukemic children who died while being treated with corticotropin After withdrawal of corticotropin clinical evidence of adrenal insufficiency as indicated by weakness fatigability, hypotension and collapse may appear These signs and symptoms may be accompanied by a relatively high eosinophil count and a relatively low 17-ketosteroid and formaldehydogenic steroid excretion in the urine It is probable that the increased corticoid secretion induced by exogenous corticotropin depresses the output of corticotropin by the pituitary gland in the same manner as administered cortisone

The effects of corticotropin and cortisone upon the integumentary system are virtually identical Corticotropin is of course not effective when applied locally There does appear to be a difference between the two hormones in their effect upon skin pigmentation In studies of patients with Addison s disease McCracken and Hall[553] using reflectance spectrophotometry observed that cortisone led to a decrease in skin pigmentation that was largely due to a diminished melanin content In patients with intact adrenal glands on the other hand the administration of corticotropin resulted in an increased melanin content of the skin, this may be correlated with the observation that darkening of the skin in man frequently occurs during corticotropin therapy It has been suggested that contamination of corticotropin by intermedin (melanophore-expanding hormone) is responsible for this phenomenon[191] although an influence of intermedin on melanin in mammalian skin has yet to be clearly demonstrated

Whereas there appears to be little difference between corticotropin and cortisone in their effects upon the EEG and psyche in man Woodbury[146] has

demonstrated a difference in their influence on the electroshock seizure threshold (EST) in rats Cortisone produced a marked and corticotropin a slight increase in EST

Extra adrenal Actions Two types of extra adrenal actions of corticotropin have been described One appears to involve the mediation of adrenal steroids in pregnancy This action is considered to be an effect of corticotropin upon placental production of corticosteroids In this regard Jailer[554] has observed a normal eosinophil response to corticotropin in 2 patients with Addison's disease during pregnancy but not during the post partum period Since it is known that the steroid level in the urine of newborn infants is extremely low it appears unlikely that the fetal adrenal gland is responsible for this change It is of interest in this connection that cortisone and hydrocortisone have recently been isolated from human placental tissue[390]

The second type of extra adrenal action of corticotropin envisages a biologic effect not mediated by adrenocortical steroids Studies in animals have been reported in which effects of corticotropin preparations have been observed in the absence of the adrenal cortex[555–557] It remains to be established whether the effects observed to date are the result of an extra adrenal action of corticotropin or of contaminating pituitary substances To date no action of corticotropin not mediated by adrenocortical steroids has been demonstrated in man

Metabolic Fate of Corticotropin

Information on the metabolism and excretion of corticotropin is meager Sayers and his co-workers[558] have shown that corticotropin disappears rapidly from the circulation after intravenous administration When normal human subjects were given 50 to 100 international units of the hormone in 30 minutes to an hour by the intravenous route it was found that elevated plasma levels of corticotropin returned to normal within 2 hours of completion of the infusion Greenspan Li and Evans[559] reported more rapid disappearance of corticotropin after intravenous injection into rats The level of plasma corticotropin fell in a logarithmic fashion and the half life of the injected corticotropin activity was found to be five and one half minutes In addition it was observed that the initial plasma concentration of the hormone immediately after injection was only 6 per cent of the theoretically expected level The disappearance of corticotropin from the circulation may be due to one or more of the following factors inactivation or catabolism distribution and tissue fixation or excretion A rapid inactivation of corticotropin *in vitro* has been reported by Pincus et al[560] When highly purified preparations were incubated with rat or human blood 40 to 70 per cent of the corticotropic activity was lost within an hour Evidence was obtained that suggested the presence of an inactivating system consisting of a heat-labile and heat-stable substance There is little doubt that circulating corticotropin is rapidly fixed by certain tissues Sonenberg and his associates[561] observed a rapid but short-lived deposition of radioactivity in the adrenal

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Whereas there appears to be little difference between corticotropin and cortisone in their effects upon the EEG and psyche in man Woodbury [118] has

found hemorrhages in the adrenal cortices of rats after intensive corticotropin stimulation were partly responsible for such fears which fortunately have not been realized Even maximal adrenocortical stimulation by the continuous intravenous infusion of corticotropin over periods as long as 10 days has given no evidence of permanent alterations in adrenal function in man

Earlier preparations of corticotropin frequently contained sufficient quantities of posterior pituitary hormones to cause overt pressor and antidiuretic effects With improved methods of purification these substances have largely been eliminated from the commercial preparations now available

Sensitivity reactions to corticotropin itself or to some factor in the preparation have occasionally been reported These reactions have been of two main types The *immediate* reaction has appeared within a few minutes of intramuscular injection or the initiation of an intravenous infusion of the hormone Its manifestations have been itching and urticaria occasionally wheezing and angioneurotic edema and very rarely anaphylactic shock [564 565] The *delayed* reaction begins several hours after the institution of corticotropin therapy by either the intramuscular or the intravenous route and consists of fever and malaise [468] These reactions have become rare now that the purity of the commercial preparations has been improved It should be emphasized, however that patients who have undergone bilateral adrenalectomy or who have Addison s disease or panhypopituitarism are much more likely to react adversely to corticotropin preparations This is particularly true if the hormone is being given by intravenous infusion [468] It appears that a responsive adrenal cortex will protect the patient to a considerable degree against a sensitivity reaction Consequently in patients with adrenal insufficiency caution should be exercised when intravenous infusions of corticotropin are given During the course of several thousand intravenous infusions we have encountered only 6 potentially serious untoward reactions Delayed febrile reactions have occurred in 2 patients with Addison s disease Urticaria and pruritus have occurred almost immediately after the start of intravenous infusions of corticotropin in 3 patients with Addison s disease and in 1 patient after the termination of a prolonged course of cortisone therapy All patients involved had received corticotropin on previous occasions It should be noted that in 3 of these patients repeated intravenous infusions of a highly purified potent preparation of corticotropin were administered without any reactions It therefore appears probable that reactions of this type are produced by inert protein rather than by corticotropin itself

Preparations and Routes of Administration

As a consequence of the extensive research devoted to the isolation of corticotropin remarkably potent and highly purified preparations of the hormone are now available It should be emphasized that both the purification and large scale production of corticotropin have been greatly facilitated by the adrenal ascorbic acid depletion method of corticotropin bioassay developed by Sayers and his associates[464] in 1948 This procedure has served

cortex of rats that had received intracardiac injections of I^{131} labeled preparations of corticotropin Radioautographs showed the radioactivity to be particularly concentrated in the inner layers of the cortical tissue Richards and Sayers[867] studied the fate of intravenously injected corticotropin in normal rats Five minutes after injection 40 per cent of the administered hormone was in the extracellular fluid and 20 per cent was fixed in the kidneys At 15 minutes a negligible amount of corticotropin was found in the extracellular fluid whereas 15 per cent remained in the kidneys A small quantity of corticotropin was detected in the adrenal glands but none in the liver or urine

Toxicity

Effects of Stimulation of the Adrenal Cortex Prolonged administration of corticotropin with resultant intense adrenocortical hyperactivity may eventually lead to the appearance of the same undesirable effects that are seen with long continued cortisone therapy (discussed in the previous section on Cortisone) As with cortisone these effects are of two types those due to overdosage of the hormone that occur during its administration and resemble one or more of the manifestations of Cushing s syndrome and tho e that follow hormone withdrawal and reflect a state of adrenal insufficiency induced by pituitary inhibition The appearance of the former effects is influenced to a considerable degree by the mode of administration of corticotropin When the hormone is given by intramuscular injection a more sustained action is achieved than that obtained with a daily eight hour intravenous infusion Consequently when patients are treated by the latter method overdosage phenomena are usually less marked and less frequent Although the effects of overdosage of corticotropin and cortisone are qualitatively similar certain quantitative differences exist At a given level of therapeutic effectiveness edema from sodium and water retention and evidence of increased androgen secretion acne and hirsutism—are often more prominent during treatment with corticotropin than with cortisone The former may well reflect the adrenocortical secretion of steroids more potent in electrolyte regulation than cortisone and the latter the direct secretion of androgenic substances

Symptoms of adrenal insufficiency that may appear upon cessation of corticotropin therapy may be mild or severe depending upon the duration of therapy level of dosage and rapidity of withdrawal Extreme care hould be exercised in withdrawal of the hormone particularly after a prolonged period of therapy The dosage should be tapered slowly with a gradual increase in the interval between doses until normal levels of endogenous adrenocortical secretion are restored and maintained In general, the duration of relative adrenal insufficiency after the termination of a long period of corticotropin therapy is less prolonged than that which follows long continued treatment with cortisone

Effects of the Preparation Itself There is a po sibility that large doses of corticotropin over long periods will in some way injure or exhaust the human adrenal cortex through 'overstimulation' The observations of Ingle[883] who

inactivation Consequently the dosage of these preparations required to produce a given level of metabolic and therapeutic activity is approximately one-third of that of some widely used types of corticotropin prepared by older methods *Despite this significant differential of effectiveness after*

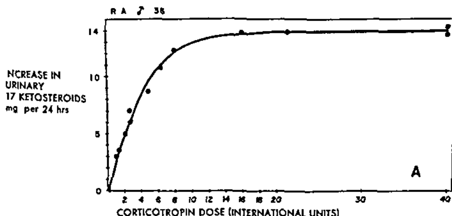


FIG 18 Dose-response curve of 17 ketosteroid excretion to increasing amounts of corticotropin administered intravenously to a normal subject over a period of eight hours

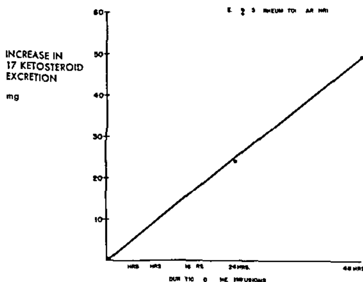


FIG 19 Time response curve of 17 ketosteroid excretion to corticotropin infused intravenously at a constant dosage of 20 units (see text) The rises in 17 keto teroid excretion are expressed in milligrams per 24 hours except for the 48 hour infusion which is *in milligrams per 48 hours*

intramuscular administration both types of preparation are equally active when infused intravenously Furthermore since both types are assayed by the Sayers test which employs the intravenous route of administration it is apparent that a wide discrepancy between the labeled potency and the

as the basis of standardization of both the international and U S P standards for corticotropin

The majority of commercial preparations of corticotropin are derived from either hog or sheep pituitary glands Potent preparations have also been obtained from beef pituitary glands and it is of interest to note the successful use of whale pituitary glands as a source of corticotropin in Norway [566] At present most preparations are remarkably free of contaminating pituitary hormones—luteotropin thyrotropin and posterior pituitary factors

Two types of corticotropin preparations are now available for therapeutic use a standard short acting preparation available either as a lyophilized powder or as a stable solution in water containing 1 per cent phenol for subcutaneous intramuscular or intravenous use, and a long acting preparation of lyophilized corticotropin incorporated in a gelatin menstruum for subcutaneous or intramuscular injection

Short-Acting Preparations Powdered preparations are dissolved in physiologic saline solution or distilled water immediately before injection Since the metabolic effects of a single injection of these preparations are comparatively brief administration must be repeated at intervals of six to eight hours to achieve *continuing adrenocortical stimulation* The eosinopenia produced by the intramuscular injection of a single dose of 25 U S P units of a lyophilized preparation of corticotropin is maximal 4 to 6 hours after injection The eosinophil level usually returns to normal after 8 to 12 hours

Since the intensity of adrenocortical response elicited in different persons may vary significantly no fixed dosage schedules can be prescribed In general an effective therapeutic response can ordinarily be produced at a total daily dosage level of 40 to 80 units administered in divided doses at intervals of six or eight hours In some cases however much higher dosages, such as 200 units daily may be required during the initial period of therapy At continuing dosage levels of 100 units per day or above undesirable physiologic or metabolic effects frequently appear Once a satisfactory clinical remission has been obtained the total daily dosage of corticotropin should be reduced to the minimal level consistent with the maintenance of a satisfactory therapeutic response For example individual doses may be reduced by 5 units daily at intervals of three to five days until a satisfactory maintenance schedule is established Subsequently the interval between doses may be lengthened but unfortunately the majority of patients continue to require two or three doses of regular corticotropin a day to achieve an effective maintenance level of adrenocortical stimulation

In the past a number of patients treated with corticotropin have exhibited increasing unresponsiveness to the hormone administered by intramuscular injection This phenomenon has been termed corticotropin 'resistance' [567] and appears to be the result of intramuscular inactivation or destruction of the hormone since administration of the same preparation by intravenous infusion to these patients produced a normal adrenocortical response However certain highly purified preparations of corticotropin such as that described by Astwood [485] have proved far less susceptible to

tropin has been shown to be a direct function of the duration of continued stimulation of the gland it was anticipated that the gel preparations would result in enhanced therapeutic effectiveness That the physiologic and therapeutic effects of a single injection of corticotropin in gelatin considerably exceed those resulting from a single injection of an equivalent dose of the lyophilized material is demonstrated in Figure 20 The blood eosinophil and urinary 17 hydroxycorticosteroid responses produced by the injection of 40 U S P units of the same lyophilized preparation of corticotropin in 1 case administered in saline solution and in another dissolved in a 16 per cent

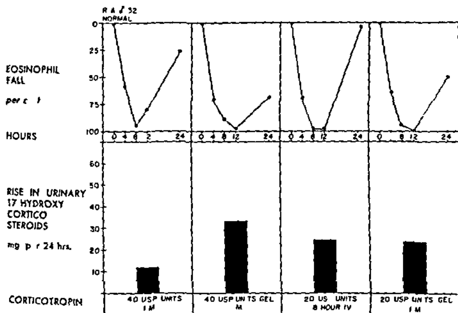


Fig 20 A comparison of the results of administration of various corticotropin preparations to a normal thirty two year-old man

gelatin vehicle are shown Because of their enhanced adrenocorticotropic activity owing to the use of highly purified corticotropin as well as to the prolonged period of action presently available corticotropin gels have arbitrarily been restandardized in terms of "clinical" or commercial units rather than U S P units Thus to elicit a therapeutic effect equivalent to that produced by the intermittent intramuscular injection of 40 U S P units per day of older lyophilized preparations a total daily dosage of approximately 14 U S P units of the highly purified corticotropin in gelatin is ordinarily required The latter preparation however is actually labeled 40 commercial units or as clinically equivalent to 40 U S P units The gel preparations are therefore labeled in terms of the clinical effect obtained rather than in terms of the actual number of U S P units of corticotropin contained in the vial Indeed the difference in the actual quantity of purified corticotropin present can be easily demonstrated by comparing the intensity of adrenocortical stimulation produced by the intramuscular injection of 40 U S P

clinical effectiveness of the two preparations may be demonstrated when they are given intramuscularly It should be emphasized, therefore that the labeled potency of hormonal preparations will be valid in general only when the route of administration employed in assaying a preparation correspond to the route by which the hormone is given therapeutically [564] Fortunately, at present the most extensively used preparations of corticotropin are so carefully prepared as to be almost equally potent by both the intramuscular and intravenous routes, and the problem of resistance is of far less significance than formerly

The intravenous route in man was first employed by Sayers et al [558] who demonstrated most of the known physiologic effects of corticotropin in 2 normal subjects after intravenous infusion of comparatively large doses of the hormone during a 30 minute period Gordon[569] subsequently demonstrated the therapeutic effectiveness of intravenously infused corticotropin in man using continuous infusions extending over several hours or days Subsequent studies[565 570] have established the intravenous administration of corticotropin as a highly effective and economical method of producing adrenocortical activation An eight hour infusion of 20 to 25 U S P units has been found to have metabolic and therapeutic effects comparable to those achieved by the daily intramuscular injection of from 100 to 150 units of lyophilized corticotropin (35 to 50 units of the highly purified preparations)

Detailed investigations of the intravenous route have delineated the pharmacologic parameters of this method of hormone administration and clarified the physiologic and quantitative aspects of adrenocortical activation [570] By means of changes in the number of circulating eosinophils and the rise in urinary 17 ketosteroid excretion as indexes of the degree of adrenocortical stimulation obtained it was demonstrated that the intensity of response produced increased with the amount of corticotropin infused up to a critical dosage over and above which little or no additional response was elicited (Figure 18) In subjects with normal adrenocortical function this critical dosage level was approximately 20 units infused over an eight hour period With a constant dose of 20 units it was demonstrated that an extension of the period of infusion from 30 seconds to 48 hours resulted in a linear increase in the intensity of adrenocortical activation (Figure 19) It is therefore clear that there is a maximal quantity of corticotropin that during a given period of time can be effective in stimulating the adrenal cortex and that the total output of adrenocortical steroids initiated by a standard dose of corticotropin varies directly with the duration of the intravenous infusion

Long-Acting Preparations To increase the duration of adrenocortical stimulation the hormone has been incorporated in a gelatin menstruum Long acting preparations of corticotropin may be administered subcutaneously or intramuscularly The gel preparations available consist of highly purified hormone prepared by modifications of the oxycellulose column method of Astwood [485] To date we have encountered no cases of resistance to these preparations

Since the intensity of adrenocortical stimulation induced by cortico-

Although treatment with DOC unquestionably prolonged the life of many of these patients, cortisone has corrected important metabolic defects not affected by DOC the facilitation of gluconeogenesis the restoration of water metabolism to normal and the correction of the electroencephalographic abnormalities of Addison's disease Appetite muscular strength and work tolerance are improved, and anemia is diminished These changes in conjunction with the remarkable sense of well being imparted by cortisone, have greatly increased the capacity of these patients to withstand the demands of an active comparatively normal existence

For maintenance therapy cortisone is administered by mouth in a dose of 12 5 to 25 mg per day Because of the frequent occurrence of mental stimulation during the early weeks of treatment it may be necessary to employ the smaller dose at first In the occasional patient who is overstimulated by even minute doses of cortisone acetate hydrocortisone is often well tolerated at a dosage level of 12 5 to 25 mg per day The concurrent administration of DOC is deemed essential for the majority of these patients

Although the oral administration of cortisone is preferred because of its obvious convenience intramuscular injection is satisfactory and may be imperative during periods of acute gastrointestinal disturbance During periods of intercurrent infection or other stress the dosage of cortisone should be elevated temporarily to a level of 50 to 100 mg per day to meet the increased hormone requirement

Patients with Addison's disease and active tuberculosis present a special therapeutic problem and provide the one situation in which cortisone therapy in the presence of active tuberculosis can be considered justified at this time The use of complete substitution therapy including cortisone in doses of 12 5 to 25 mg per day has had no deleterious effects upon the tuberculous process Indeed the over all physical and psychic status of these patients has been materially improved

Classic adrenal crisis has become increasingly uncommon since the advent of cortisone for routine replacement therapy Since the primary requirement of these patients is an immediate elevation of adrenocortical hormone in the blood and tissues the intravenous administration of hydrocortisone or cortisone is the procedure of choice An initial rapid intravenous injection of 50 mg of hormone followed by a continued intravenous infusion at a rate of approximately 10 mg per hour produces a prompt and effective therapeutic response In the presence of marked dehydration and hypotension moderate doses of DCA in oil (5 to 10 mg on the first day and 2 5 to 5 mg daily thereafter) should also be administered

The availability of cortisone has made complete bilateral adrenalectomy possible in treatment of hypertension and neoplastic diseases The following program has proved eminently successful for the support of patients during operation

Cortisone 100 mg intramuscularly 12 and 2 hours before operation

Hydrocortisone (or cortisone) 10 mg per hour intravenously, during and four to six hours after operation

units of purified corticotropin in gelatin and 40 *clinical* units of an identical preparation the intensity of adrenal activation elicited by the preparation calibrated on the basis of the U S P standard is at least twice as great as that calibrated in terms of clinical equivalents In summary, highly purified preparations of corticotropin injected extravascularly in a gelatin menstruum exert a metabolic and therapeutic effect approximately three times as great as that of an equivalent quantity of the older less pure lyophilized preparations of the hormone injected intramuscularly in divided doses

The intramuscular or subcutaneous injection of approximately 40 clinical (or commercial) units of corticotropin gel elicits an adrenocortical activation approximately equal to that produced by the intravenous infusion of 20 U S P units of lyophilized corticotropin over an eight hour period (Figure 20) The administration of 80 to 120 clinical units in gelatin results in approximately the same degree of adrenocortical stimulation produced by the continuous 24 hour infusion of 20 to 40 U S P units of lyophilized corticotropin The maximal effect of a single dose of corticotropin gel 20 to 40 units occurs from 15 to 18 hours after injection The total duration of effect however extends into the succeeding 24 hour period It is therefore apparent that the administration of these amounts of corticotropin gel in a single daily injection has a continuous effect upon the adrenal cortex For this reason overdosage effects are far more likely to occur during a prolonged course of corticotropin gel administration than during the daily eight-hour administration of intravenous infusions Similarly the margin between an optimal dose of the gel and a dose capable of producing a significant degree of undesirable side effects may be quite narrow and dosage must therefore be precisely adjusted

It is apparent that the presently available preparations of corticotropin in gelatin provide a highly effective means of producing intensive adrenocortical activation Because of their convenience it seems quite evident that these preparations should prove highly effective in the initiation of hormonal therapy and particularly efficient in prolonged courses of maintenance treatment In the latter connection it is of interest that patients with chronic inflammatory diseases susceptible to the effects of steroid and corticotropin treatment who are successfully maintained on comparatively large doses of cortisone or hydrocortisone may often be successfully maintained on comparatively small quantities e g 10 to 20 U S P units of corticotropin in gelatin injected once daily and in some cases once every two days In addition the single daily injection of 40 to 80 U S P units of the gel preparations for two days constitutes an excellent test of the integrity of adrenocortical function as measured by changes in circulating eosinophils and a rise in the urinary output of adrenocortical steroids

Clinical Uses of Cortisone, Hydrocortisone and Corticotropin

Specific Replacement Therapy

Primary Adrenal Insufficiency The use of cortisone has greatly improved the effectiveness of replacement therapy in patients with Addison s disease [47]

Although treatment with DOC unquestionably prolonged the life of many of these patients cortisone has corrected important metabolic defects not affected by DOC the facilitation of gluconeogenesis the restoration of water metabolism to normal and the correction of the electroencephalographic abnormalities of Addison s disease Appetite, muscular strength and work tolerance are improved, and anemia is diminished These changes in conjunction with the remarkable sense of well being imparted by cortisone have greatly increased the capacity of these patients to withstand the demands of an active comparatively normal existence

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Cortisone 100 mg intramuscularly 12 and 2 hours before operation
Hydrocortisone (or cortisone) 10 mg per hour intravenously during and four to six hours after operation

Cortisone, 50 mg intramuscularly every six hours on the first post operative day

Cortisone 50 mg intramuscularly every 8 hours on the second and third postoperative days and every 12 hours on the fourth and fifth post operative days

Cortisone 25 mg by mouth every six hours on the sixth postoperative day and thereafter gradually reduced to maintenance levels of 12.5 to 25 mg twice daily

Maintenance of the adrenalectomized patient is in general similar to that of the patient with spontaneous primary adrenal insufficiency The majority of patients can be successfully maintained on a regimen consisting of 37.5 to 50 mg of cortisone per day in addition to 3 to 6 Gm of supplementary sodium chloride This program is especially desirable for patients who have undergone adrenalectomy because of hypertensive cardiovascular disease since on theoretic grounds the use of DOC is undesirable On the other hand in normotensive patients with metastatic carcinoma of the prostate or breast the use of DOC is often advisable although the requirement of some of these patients is considerably less than that of most patients with Addison's disease

Secondary Adrenal Insufficiency Since adrenocortical hypofunction may be an important consequence of anterior pituitary failure stimulation with corticotropin appears to offer the physiologically ideal type of substitution therapy Experience to date however has been relatively unsatisfactory because of the need for daily injections of hormone and the development of corticotropin resistance[571] The simplicity and effectiveness of cortisone by mouth make it at present the treatment of choice in secondary as well as primary adrenal insufficiency The dosage is identical with that described for the primary type Patients who are incapable of maintaining adequate electrolyte balance on cortisone alone should receive DOC testosterone and thyroid are also given as indicated

Diagnostic Use

Adrenal Insufficiency Corticotropin has been used as a diagnostic agent in the evaluation of adrenocortical function since it provides a comparatively simple and specific test of the capacity of the adrenal cortex to respond to its natural activator[45,466] The accuracy of the procedure depends upon the validity of the indexes employed the simplest of which is the change produced in the level of circulating eosinophils Whereas a significant eosinopenia after the administration of corticotropin is a reliable index of adrenal activation it should be emphasized that the level of blood eosinophils may fall in response to other pharmacologic agents or to stress without necessarily involving a detectable increase in the rate of adrenal hormone secretion[2] Therefore we recommend that *in the final evaluation of adrenocortical function changes in the excretion of urinary steroids be measured in addition to changes in circulating eosinophils*

The most convenient screening test consists of measuring the change in circulating eosinophils four hours after the intramuscular injection of 25 U S P units of a lyophilized corticotropin preparation A fall of 50 per cent or more constitutes a normal response It is apparent that an adequate number of eosinophils must be present before changes in the cell count can be *considered statistically reliable*[57] *that the eosinophil fall produced must* exceed that due to normal diurnal variation[573] and that the corticotropin preparations used must be potent Furthermore this test should not serve as the sole criterion of the state of adrenocortical responsiveness

For a more critical evaluation of adrenocortical reserve a vigorous and more prolonged adrenal stimulation must be employed Two alternative procedures are currently used The first is continuous intravenous infusion of 20 to 25 units of corticotropin during an eight hour period on two consecutive days[574] In this test a normal response consists of an 85 to 100 per cent fall in eosinophils and a significant increase in the urinary output of 17 hydroxy corticosteroids[79] (average normal rise 14 mg per 24 hours on the first day and 24 mg per 24 hours on the second) and 17 ketosteroids (average normal rise 4 4 mg per 24 hours on the first day and 8 7 mg per 24 hours on the second) The other is intramuscular injection of corticotropin gel at a dosage level of 60 to 80 clinical units daily on two consecutive days The responses produced are comparable to those achieved after the intravenous test previously described

The adrenocortical response to corticotropin in patients with adrenocortical insufficiency secondary to pituitary failure is variable depending upon the extent and duration of atrophy In the presence of marked adrenal involution either spontaneous or induced by cortisone or hydrocortisone a characteristic pattern of response may be of diagnostic aid Initially both the eosinophil and urinary steroid changes are subnormal being followed by a progressive increase in the intensity of response In some cases as long as five days of corticotropin administration may be required to produce a normal level of adrenal response

Bilateral Adrenal Hyperplasia The demonstration by Wilkins et al[575] of the therapeutic effectiveness of continued cortisone administration to patients with bilateral adrenal hyperplasia has suggested the possibility of differentiating adrenal tumor and adrenal hyperplasia in patients with virilization It was recently demonstrated that the prolonged administration of cortisone to patients with adrenocortical tumors in contrast to those with bilateral hyperplasia fails to produce a persistent depression of 17 keto steroid excretion[576,577] (Figure 21) Dosage schedules are discussed below under Adrenocortical Inhibition

Diabetes Mellitus The appearance of sustained hyperglycemia and glycosuria during treatment with cortisone hydrocortisone or corticotropin is considered to reflect a limited reserve capacity of the pancreatic islets to augment the level of insulin secretion Therefore patients who exhibit a diabetic response to corticotropin or steroid therapy may justifiably be considered cases of latent diabetes mellitus It is suggested that the response to

cortisone hydrocortisone or corticotropin should be investigated more thoroughly as a diagnostic aid in the detection of latent diabetes mellitus It should be recognized of course that glycosuria alone may reflect only the action of these hormones on renal function

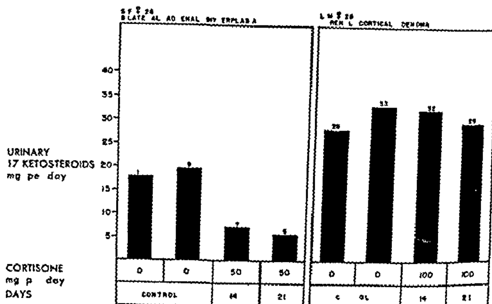


FIG 21 Adrenal inhibition with daily intramuscular injections of cortisone (Note contrast between hyperplasia and tumor)

Adrenocortical Inhibition

The capacity of cortisone to depress the secretory activity of the adrenal cortex has prompted its use in the treatment of the adrenogenital syndrome due to bilateral adrenal hyperplasia The careful studies of Wilkins et al [61, 286, 3, 9] have established the effectiveness of this form of therapy Although the suppression of adrenal secretion should be as complete as possible it is desirable to use the smallest dose of cortisone commensurate with continued suppression of adrenal activity to avoid untoward side effects With the urinary output of 17 ketosteroids as a guide doses must be determined for each patient Treatment is usually initiated with intramuscularly injected cortisone at a dosage level of 50 mg per day for older children and 25 mg per day for younger children and infants Maximum suppression of urinary ketosteroids occurs within 5 to 10 days after which maintenance doses should be instituted The final level of 17 ketosteroid excretion obtained represents the balance between endogenous secretion from the adrenal cortex and the metabolic conversion of administered cortisone to urinary 17 ketosteroids In general a somewhat greater quantity of 17 ketosteroids is derived from orally administered cortisone than from an equal dose injected intramuscularly For older children maintenance doses of 25 mg per day are usually sufficient whereas in infants and younger children smaller doses are ordinarily effective The maintenance suppressive doses of orally

administered cortisone are approximately two or three times as great as those given by the intramuscular route

Although it is too early to assess the long term effect of cortisone in bilateral adrenocortical hyperplasia the clinical results thus far observed are encouraging Hirsutism has decreased menstrual cycles are usually re established and the breasts may undergo progressive development Hyper ten ion may significantly decrease and pigmentation ordinarily recedes

Pharmacologic Use

Cortisone hydrocortisone and corticotropin have provided clinicians with a triad of therapeutic agents possessing a cope of physiologic and pharmacologic activities equaled by few drugs It is apparent therefore that the physician employing these agents must possess a sound understanding of their multiple metabolic activities if the greatest benefit is to be derived and if undesired effects are to be minimized

It was inevitable that the initial reaction to the widespread use of these agents in the treatment of crippling diseases previously refractory to avail able pharmacologic agents should be associated with considerable enthusi asm Although time and experience have exerted a tempering effect upon the over all evaluation of their therapeutic efficacy it is clear today that they have achieved a definite area of clinical usefulness In certain specific situa tions their u e may be lifesaving In others they provide a nonspecific means of controlling at least temporarily many metabolic inflammatory and allergic disorders Although these agents do not provide a *biologic cure* for a single known entity their careful but imaginative use has created numerou and effective therapeutic approaches where none had previously exi ted It must be emphasized however that the hormones serve in no way as substitution for standard measures of supportive treatment

In contrast to the relatively well standardized program of substitution therapy employed in patients with adrenal and pituitary insufficiency it is difficult to establish arbitrarily therapeutic programs for the wide range of disorders in which the hormones are used nonspecifically Optimum dosage is not fixed the metabolic and clinical responses of the patient although generally predictable are highly variable It is therefore mandatory that the course of therapy undertaken with these agents be truly individualized Furthermore, it is essential that the therapeutic effect obtained be evaluated in terms of the over all metabolic changes produced in order to establish the dosage level that will provide maximal therapeutic benefits with minimal undesirable side effects

Patients suitable for hormonal therapy may be classified as follows those in whom this therapy may be lifesaving or may lead to a significant pro longation of life e g intensive hormonal therapy is capable of salvaging at least temporarily the majority of patients with severe pemphigus those in whom hormonal treatment results in the restoration or preservation of cer tain essential functions e g , the use of these agents in certain destructive inflammatory ocular diseases may prevent serious or total loss of vision

those with certain acute self limited inflammatory or allergic disorders, who may be relieved of discomfort and even disability by the administration of suppressive doses of steroids or corticotropin during the natural course of these disorders e g pruritus erythema and exudation may be relieved in certain patients with contact dermatitis and those with chronic disease in whom steroid therapy may delay or modify the development of either destructive or fibrotic sequelae as in rheumatoid arthritis It should be reemphasized that the decision to employ hormonal therapy in a chronic disease demands a comparative evaluation of the potential gains and risks involved Thus a maintained conversion of patients with rheumatoid arthritis from Class III* (functional capacity limited to little or none of usual duties) to Class II* (functional capacity adequate for normal activities despite handicaps of discomfort or limited motion of one or more joints) may well warrant the induction of a mild state of hyperadrenalism on the other hand eliminating the chronic and relatively stationary lesions of discoid psoriasis rarely justifies the protracted use of hormonal therapy Similarly hormonal treatment is frequently indicated for the control of acute and severe exacerbations of a chronic disorder in which there is a reasonable possibility of spontaneous remission or in which standard methods of treatment may suffice to control the disease except during acute episodes The use of steroid or corticotropin therapy for the acute hemolytic crisis of acquired hemolytic anemia exemplifies this type of treatment

The precautions to be taken before or during long term cortisone and corticotropin treatment have been described in the section on Cortisone It should be emphasized that laboratory data are in no way a satisfactory substitute for frequent careful clinical observations

Dosage Dosage schedules cannot be arbitrarily established but must be determined on the basis of the clinical response obtained In general an effective initial response to corticotropin is produced by the intramuscular administration of 50 to 100 U S P units of a lyophilized preparation in divided doses at intervals of six to eight hours the intramuscular or subcutaneous administration of 40 to 80 clinical units of corticotropin in gelatin daily or the daily intravenous infusion over an eight hour period of 20 to 25 U S P units of a lyophilized preparation Once an adequate clinical response is produced the total daily dose should be gradually reduced to maintenance levels The ultimate objective in long term therapy is to establish the minimal maintenance dose capable of sustaining a clinical remission Should the clinical response to administration be inadequate the production of an adrenocortical response should be verified

For patients treated with cortisone or hydrocortisone an initial daily dose of 150 to 300 mg is ordinarily effective With intramuscular administration a single daily injection is usually adequate When the oral route is employed the hormone should be administered at intervals of six to eight hours Once a satisfactory clinical response is established dosage should be reduced gradually by decrements of 10 to 12 5 mg until the lowest dosage level

* Classification of the American Rheumatism Association

capable of maintaining a suitable therapeutic response is attained The importance of exercising great care in tapering the dose of cortisone or corticotropin when termination of hormonal treatment is contemplated was discussed in the previous sections on Cortisone and Corticotropin

During hormonal therapy certain readily observable alterations in the patient's clinical condition serve as practical guides for evaluating the intensity of the metabolic and therapeutic response An improved sense of well-being and an increase in appetite may appear early in the course of therapy Fever is ordinarily reduced often within hours of the initiation of treatment Conversely a rise in temperature during a program of dosage reduction directly suggests either an inadequate dosage level or a superimposed complication The disappearance of pain and the inhibition of the classic signs of inflammation reflect a satisfactory therapeutic effect A suppression of the patient's inflammatory responses however imposes upon the physician the obligation of continual alertness to the possible occurrence of a masked infection

In most cases the type and severity of a pathologic process do not determine the hormonal agent to be employed In some cases the threat of complications may justify the choice of one agent For example in the presence of marked hypertension or cardiac decompensation the use of cortisone or hydrocortisone may be considered preferable because of a somewhat less intense initial sodium and water retention than that encountered during corticotropin therapy On the other hand certain patients with severe disseminated disease such as pemphigus have sometimes not responded well to doses of cortisone as large as 500 mg per day but have demonstrated a prompt improvement during intensive treatment with corticotropin For the local treatment of joint eye or skin disease hydrocortisone has been found to be considerably more effective than cortisone as pointed out in the section on Hydrocortisone

Musculoskeletal Disease One of the earliest instances of the therapeutic use of adrenal hormones in human disease was the trial by Soffer et al [578] in 1948 of corticotropin in patients with myasthenia gravis In the majority of patients the disease is aggravated during hormone administration in rare cases death has occurred After hormone withdrawal however muscular function may improve resulting in a decreased requirement for neostigmine In view of the potential dangers involved treatment of myasthenia gravis with these agents is not recommended except in highly specialized hands

A decrease in myotonic response has been observed during intensive cortisone and corticotropin therapy in patients with dystrophia myotonica but without significant improvement in the muscular or visceral dystrophies Improvement in muscular strength and endurance has been described in the muscular dystrophy of menopausal women [4] Treatment of other forms of myopathies has not proved beneficial

Cortisone hydrocortisone and corticotropin may be extremely useful in the treatment of bursitis and calcific tendinitis [579] The intravenous infusion of corticotropin over an eight hour period for one or two days often provides

almost complete relief from pain, accompanied by a marked increase in mobility The local injection of hydrocortisone into inflamed bursas in a dose of 25 to 50 mg ordinarily results in prompt clinical improvement The therapeutic results of manipulation of the "frozen" painful shoulder are considerably enhanced by the concomitant administration of steroid hormones or corticotropin For example the continuous intravenous infusion of corticotropin during a period of 18 to 24 hours before manipulation and for a similar period after the procedure may markedly reduce pain thereby facilitating both passive and active mobilization of the joint

Diseases of the Nervous System The effects of cortisone and corticotropin in various disorders of the nervous system have been reviewed by Merritt [550] No beneficial effects have been obtained in patients with amyotrophic lateral sclerosis anterior poliomyelitis cerebromaculodegeneration Wilson s disease and Parkinson s disease No improvement has occurred in the majority of patients with multiple peripheral neuritis and idiopathic epilepsy

Approximately one third of the patients with multiple sclerosis treated with cortisone or corticotropin have been reported to show changes suggestive of improvement in the ataxic spastic paretic and acute visual manifestations In most cases improvement has been temporary The effects of prolonged therapy on the ultimate course of the disease remain to be determined The difficulties of evaluating pharmacologic agents with potent nonspecific effects in a chronic disease characterized by wide spontaneous fluctuations in clinical course are obvious

The most important application of hormonal therapy in nervous system disorders has undoubtedly been the successful treatment of acute optic and retrobulbar neuritis occurring either as a manifestation of multiple sclerosis or as an independent phenomenon [551] A lessening of pain a decrease in the size of scotomas and a significant increase in visual acuity have been achieved in a high percentage of cases Although spontaneous remissions certainly occur in this disorder the frequency with which good therapeutic results have been achieved during cortisone or corticotropin therapy suggests that these agents are indeed responsible Quinn and Wolfson[55] have emphasized the fact that prolonged treatment at high dosage levels may be effective even in chronic apparently irreversible cases of optic neuritis Once a significant degree of improvement is induced dosage may be gradually reduced to maintenance levels

Metabolic Disease The early studies of Hellman[553] and of Wolfson and his associates[554] showed that the administration of corticotropin could terminate an acute attack of gouty arthritis unfortunately withdrawal of hormone was frequently followed by an acute relapse These observations have been repeatedly confirmed Although an attack of acute gouty arthritis can usually be effectively and rapidly relieved by the intramuscular injection of 80 to 120 clinical units of corticotropin in gelatin or by the continuous intravenous infusion of 20 to 25 U S P units of corticotropin over a period of 8 to 24 hours it is essential that colchicine administration be instituted

simultaneously to prevent a recurrence of the attack after hormone withdrawal[585] The relief produced appears to depend chiefly upon the antiphlogistic action of the hormones since it has been frequently demonstrated that the acute attack may subside before a significant degree of uricosuria has been observed Since symptomatic relief may be rapidly achieved the availability of cortisone and corticotropin for the treatment of acute gouty arthritis constitutes a significant therapeutic advance[586] particularly in patients who respond poorly to colchicine therapy It appears preferable at present to depend primarily upon nonhormonal uricosuric agents such as salicylates and Benemid for the treatment of interval gout

The findings of Szilagyi et al [587] concerning the beneficial effect of adrenocortical hormones in patients with acute thyroid crisis suggest that the intravenous infusion of cortisone or hydrocortisone may prove to be of value in the treatment of this disorder

The principal conditions in which cortisone and corticotropin have been used and the results obtained in these many and varied diseases are reviewed in succeeding chapters of this volume

The discovery and preparation of the adrenocortical steroids and corticotropin have presented the medical profession with a potent and challenging group of new therapeutic agents The important metabolic effects mediated by these hormonal preparations can be appreciated fully only by physicians who are prepared to devote time and effort to improving their understanding of the intermediary chemical reactions that permit man to adapt successfully to an ever changing environment Not only have these hormones provided specific substitution therapy and diagnostic aids in complex endocrinopathies but also their effectiveness in modifying the inflammatory response of tissues may ultimately increase understanding of the pathogenesis of many widespread and serious disorders The successful use of hormonal therapy in disorders other than the specific endocrine deficiencies requires careful judgment and the most effective application of the art of healing It is apparent that the ready availability of these hormonal preparations has presented the medical profession with a serious challenge which is heightened by the intense interest of the general public in advances medical It is hoped that the material presented in this review may provide a basis for increasing the usefulness of these substances as important pharmacologic agents

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3

Rheumatoid Arthritis and Other Rheumatic or Articular Diseases

Philip S Hench and L Emmerson Ward

During the past six years the application of cortisone hydrocortisone and corticotropin to basic researches to general medicine and to the investigation and treatment of rheumatic diseases has aroused considerable interest since it has provided new data related to physiology metabolism and therapeutics and has led to formation of new concepts of disease But it has also provoked controversy and confusion Some of the latter is understandable in view of our limited experience and knowledge of basic mechanisms but some is needless or fruitless

Although understanding of the subject is still incomplete what is known should be sufficient to dispel undue concern to explain certain controversies to eliminate some of the differences of opinion and to serve as a practical guide for the safe and effective use of these hormones* in selected cases of rheumatic diseases

Application of the Hormones to the Rheumatic Diseases

The progress that has been made in the clinical application of cortisone hydrocortisone and corticotropin their future role in the study and treatment of disease especially the rheumatic diseases and the reasons for major controversies can perhaps be best appreciated if we divide the clinical work of 1948 to 1953 into three distinct and definitive phases

Phase 1 Preliminary Investigations and Early Confirmations (1948–1949)

Preliminary Investigations In the summer of 1948[1] the first synthetic compound E (Kendall) was given to 3 or 4 patients with Addison s disease [2–4]

* In this volume the terms *hormones* and *hormonal* or *adrenocortical therapy* used in a general sense refer only to those hormones under discussion namely cortisone hydrocortisone and corticotropin unless otherwise specified

From the Division of Medicine Mayo Clinic Rochester Minnesota

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This was considered rational as a new form of replacement therapy In September 1948 compound E or cortisone,* in February 1949, adrenocorticotropic hormone or corticotropin,† and in April 1949, compound F or hydrocortisone‡ were used effectively in certain patients with rheumatoid arthritis[5–9] We gave these hormones on the assumption that cortisone or a related substance might be the "antirheumatic and antiallergic substance X which during pregnancy, jaundice, or starvation often suppresses rheumatoid arthritis as well as such conditions as asthma hay fever, egg sensitivity and migraine[5 9–1]

Chosen for the first administrations were patients with severe but reversible rheumatoid arthritis For our first patient, Kendall and Hench decided to use daily intramuscular doses of 100 mg of cortisone (free alcohol) Later, daily doses of 50 to 200 mg were given Corticotropin 100 units was administered intragluteally a dose given previously to a normal person,[13] our later doses varied from 45 to 140 units daily Such doses demonstrated that these hormones were antirheumatic and anti inflammatory They reduced articular inflammation notably—but sometimes incompletely—suppressed rheumatic symptoms and tended to normalize many of the metabolic and biochemical alterations of rheumatoid arthritis

To determine whether these daily doses could be tolerated indefinitely and how long symptoms would remain in abeyance after discontinuance of administration we and our colleagues Kendall Slocumb and Polley gave the hormones either continuously for more than six months or in single or repeated short courses If the doses first used were continued indefinitely certain undesirable effects developed often progressively, when shorter courses were ended relapses commonly occurred, sometimes with withdrawal reactions

To test the chemical specificity of cortisone (free alcohol) and corticotropin, other substances were used Markedly antirheumatic were cortisone acetate and hydrocortisone (free alcohol) given intramuscularly and a special concentration of adrenocortical extract containing a mixture of cortisone and hydrocortisone in capsules taken orally But certain compounds related chemically to cortisone and hydrocortisone and smaller concentrations of adrenocortical extract possessed no antirheumatic potency

To test the clinical specificity of the effective hormones we soon gave them to a few patients with rheumatic fever lupus erythematosus tuberculous arthritis psoriatic arthritis polyarthritis with ulcerative colitis osteoarthritis and other conditions[5–9 14 15]

Certain tentative opinions were derived from the use of the hormones in 42 patients 23 of whom had rheumatoid arthritis It was suggested that the antirheumatic properties of the steroid structure depend upon the presence of a ketone group at carbons 3 and 20, either a ketone or a hydroxyl group at carbon 11, a hydroxyl group at carbons 17 and 21 and a double bond

* Supplied by Merck & Co Inc
† Supplied by The Armour Laboratories
‡ Supplied by The Upjohn Company

between carbon atoms 4 and 5 [16] Since the hormones exerted wide physiologic influence and affected bodily systems and tissues both in health and disease the effects had to be regarded as general or nonspecific But speaking clinically they were classified as group specific[9] since certain types of diseases were especially responsive The hormones provided their antirheumatic and other effects by suppressing the reactions of tissues to the disease [9]

Confirmatory Studies Because of continued scarcity during 1949 cortisone or corticotropin was given to only 45 additional rheumatoid patients Results appeared in 18 reports from 12 groups in the United States Sweden and Denmark [17–34] Of these 45 patients 95 per cent were benefited usually markedly

These reports confirmed the original studies and included some new observations on the effect of the hormones upon electroencephalograms (EEG's), the electrophoretic pattern of serum proteins and wound healing The most important observation was that of Boland and Headley [24] that doses of cortisone (50 mg daily) smaller than those required in our severe cases (about 100 mg daily) were effective against mild or moderate rheumatoid arthritis

Early Conjecture about Mode of Action An Academic Difference of Opinion Early investigators were in notable agreement in their evaluation of the clinical and metabolic effects of these hormones upon rheumatoid patients and in their conjectures about the manner of the hormonal effect But concerning the possible mode of action of the hormones a division of opinion arose

In our first reports[5 6 9] the idea was suggested that rheumatoid and other responsive patients might have some unidentified type of adrenocortical deficiency Thorn and associates formed a tentative opinion that the antirheumatic effect of these hormones resulted not from correction of adrenal deficiency but from pharmacologic action Effective therapy is only attained when the level of hormone is increased to supernormal levels [1] Ragan Grokoest and Boots[28] also expressed a similar opinion

Our group noted that the adrenals of at least some rheumatoid patients were unresponsive to corticotropin and that urinary concentrations of 17 ketosteroids of rheumatoid patients before administration of any hormone were sometimes low [9 35] Without attempting to interpret these data we amplified slightly our original conjecture and suggested that if a deficiency of cortisone were present in rheumatoid arthritis it might be a relative, not an absolute deficiency perhaps one concerned with increased destruction or increased tissue requirement for corti one rather than decreased production [8 9]

This early difference of opinion seemed at the time to be largely academic because the opposing propositions were then beyond proof But what began as conjectures and academic debate whether the hormones act physiologically or ' pharmacologically had rather far reaching consequences

Contributions of Synthetic Chemists and Pharmaceutical Manufacturers The contributions made by synthetic chemists and by pharmaceutical manufacturers especially by the men associated with or advising Merck &

Co Inc and The Armour Laboratories, cannot be overestimated In the fall of 1948 and spring of 1949 they set up production schedules which were regarded as impossible of attainment and then broke one record after another As a result by the spring of 1950 relatively large amounts of cortisone and corticotropin were available or potentially so The Federal Food and Drug Administration introduced the next phase in the clinical application of these hormones on June 3 1950 by releasing available amounts to the medical profession for administration to patients to be studied and treated under hospital conditions, soon thereafter unrestricted use was permitted

Phase 2 The Period of Trial and Error (1950–1953)—Wide, Essentially Unrestricted Use of These Hormones

Phase 2 was characterized by the unrestricted and generally empiric use of the hormones for countless clinical trials in the field of rheumatic diseases and general medicine It was also marked by the energetic but futile search for substitutes for cortisone hydrocortisone and corticotropin

Physicians who began early in this period to use these hormones against rheumatoid arthritis sought answers to three main questions (1) How do these hormones work? (2) Can they be used to provide a practical safe form of treatment? (3) What initial dose schemes should be used?

It is helpful to recall the circumstances under which these hormones were introduced for widespread use During Phase 1 certain popular interpretations gave to many patients and to some physicians the erroneous impression that use of these new hormones for rheumatoid arthritis was comparable in several ways to that of insulin for diabetes For a moment therefore we should like to compare in an oversimplified manner the introduction of cortisone and corticotropin into general medicine with that *of insulin*

Before insulin was discovered in 1921 a large fund of knowledge concerning carbohydrate metabolism and its relation to the pancreas had accumulated as the result of a half century of metabolic and clinical investigations *Then came the discovery and production of insulin in such an orderly* sequence that the direction of subsequent investigations was mostly forward Once insulin was available its physiologic activity was found to be largely as anticipated In general insulin did not notably influence many diseases or symptoms other than those it had been expected to affect From the standpoint of practical utility its use could be governed and its results measured daily by simple standardized laboratory procedures already available

In contrast was the situation with regard to the discovery of cortisone (1935) and corticotropin (1933–1943), and their clinical application (1948) to rheumatoid arthritis and other conditions If some extra articular organ controls the fate of arthritic joints its identity is unknown As for the tissue sources of these hormones the basic physiologic discoveries related to the anterior pituitary and adrenal cortex, though of paramount importance, were rather recent [28–44] except *for Addison s work and only a rather sketchy* interpretation had been made

Owing in part to limited supplies of cortisone and corticotropin but even

more to the fact that animals do not develop rheumatoid arthritis or several of the other diseases responsive to these hormones [49-51] none of the excellent experimental work had conditioned physiologists or endocrinologists to the physiologic versatility of these hormones and their field of clinical usefulness was regarded as limited [16 50-53] Thus when preliminary evidence of their broad clinical effects was obtained there was no groundwork for clinical application comparable to that for insulin Unavailable were simple laboratory tests by which the basic clinicophysiologic effects of cortisone or corticotropin could be measured carefully or directly Hence while physicians have been using the new hormones in practice physiologists and clinical investigators have had to work as it were forward and backward simultaneously

Divergent Policies of Dosage During Phase 2 many physicians were of course not content to use the hormones empirically or routinely they wanted not only an optimal dose scheme but data on the mode of action But no optimal scheme had been developed and opinions about the mode of action (physiologic versus pharmacologic) were merely conjectural Nevertheless these preliminary conjectures were elevated by some to the status of considered theories a status for which they had not been intended In this manner the two divergent policies regarding dosage originated Consequently one group of physicians the so-called pharmacologically minded has used and continued to recommend rather high doses large enough to get a real clinical effect even though the cost be a fairly definite but controllable hypercortisonism The other group the so-called physiologically minded which includes our group has recommended use of smaller and smaller doses to avoid significant hypercortisonism doses which certain other investigators have regarded critically as producing merely the effect of a super aspirin

The third and largest group is comprised of physicians who less interested in unproved theories than the others but no less concerned about their patients have used the hormones empirically modifying their dose schemes as experience dictated Our experience with cortisone treated patients referred to the Mayo Clinic suggests that many of these physicians have tended toward overdosage rather than underdosage This situation prompted development of multiple plans of administration and dosage

Other Problems During the four years of Phase 2 many other problems and choices confronted physicians the hormone of choice the route of administration the optimal length of treatment management of undesirable effects and withdrawal reactions evaluation of so-called substitutes for or potentiators of cortisone and the problem of refractoriness or of sensitivity to the hormones No wonder many different and sometimes conflicting recommendations were made only to add to the confusion After the early results which were often unsatisfactory because of over or under dosage some physicians even asked Are cortisone and corticotropin really here to stay?

Other points debated widely during Phase 2 concerned the practicality of hormonal therapy for a chronic rheumatic disease such as rheumatoid arthritis To what extent could the hormones be used effectively but safely?

Should they be regarded as practical forms of treatment for rheumatoid patients, or merely as tools for research?

The main debate began and largely ended during Phase 2, but the prologue took place in 1949 In our preliminary report[6] we cautioned "Much more experience is needed before we shall know how effective or safe the prolonged administration of compound E will be" We carefully advanced the hormones as research tools but not (at that time) as remedies Various other early workers also adopted this conservative attitude [17-21, 154-56] But most of the 1949 reports were less cautious and referred to use of cortisone and corticotropin in rheumatoid arthritis as treatment, probably without the authors meaning to start a debate or to imply that they were taking a stand on the subject [-30, 34, 57-59] Nevertheless the debate was starting and to discourage practitioners from forming premature opinions without adequate experience we stated repeatedly that the use of these hormones should be considered an investigative procedure not a treatment [9, 60, 61]

Discussion of the value of these hormones as practical agents was largely academic in 1949 because they could not be obtained for general use But as their availability increased and as more reports on their short or long term effects appeared a few conservative critical rheumatologists in late 1950 and January 1951 cautiously approved them as practical remedies in *selected* cases of rheumatoid arthritis [1, 6-66]

For all practical purposes the debate is now over and the majority opinion (favoring the practical compromise use in selected cases) is recorded in the literature The point under discussion today is no longer if but when and how best the hormones can be used During the four years of Phase 2 much progress was made toward physiologic application of these hormones, so much that the nervous empiricism of those days is behind us and we are entering a new phase

Phase 3 Current (1952–)

The characteristic feature of the present phase is the purposeful application of the hormones in a 'paraphysiologic' manner Phase 2 overlaps and still overshadows the emerging Phase 3

Even if Phase 3 so far has been noteworthy more for its modification of principles and policies than for its greater therapeutic successes or proximity to the goal of true physiologic use of the hormones it represents a distinct advance in that a trend is developing which as further knowledge permits us to exploit it, holds considerable promise for the future

Pharmaceutical chemists of several companies and many clinical investigators have contributed to the developments and refinements responsible for Phase 3 Since these developments originated not simultaneously but consecutively, the beginning of the improved attitude toward hormonal usage can be placed with difficulty We have chosen, perhaps somewhat arbitrarily the year 1952 because its literature showed evidence of maturity a meeting of minds, a willingness to modify theory in the light of practice a more unified comprehension of both the usefulness and limitations of hormonal therapy

As the importance of individualized treatment has become clearer the variety of hormonal preparations and dosage methods is no longer a source of confusion but a matter of great usefulness and convenience In lieu of a single all purpose plan of dosage several different schemes each possessing advantages are available for individualized application The chosen preparation and dose scheme can each be tailored to the requirements of a given case

Basic research will undoubtedly provide formulas for physiologic application of the hormones but even when that time comes physicians will probably still find it useful to individualize in order to obtain a pharmacologic effect in one case, a physiologic effect in another and an intermediate or paraphysiologic effect in a third For the rheumatoid patient the best that can be accomplished now (less and less empirically) is an incomplete but increasingly successful reasonably safe approximation of the physiologic state For this more refined and individualized application the term *paraphysiologic* seems appropriate, for it symbolizes today s compromise between the pharmacologic and the physiologic recognizes the inadequacies of the present, and points to the target of the future

Review of Hormonal Treatment of Rheumatoid Arthritis (1948–1953)

Diversity of Materials and Methods

Of the hundreds of reports directly or indirectly related to the use of the hormones in rheumatoid arthritis a large representative number have been reviewed It would be gratifying if one could tabulate the major data therein treat them statistically and end with clear cut results and firm conclusions But analysis of the reports of the first five years has been difficult because of the diversity of materials and methods

Hormones Used During 1948 and 1949 significant amounts of only two active preparations were available cortisone acetate Merck and corticotropin Armour both for intramuscular use For research purposes small amounts of four other effective preparations were made cortisone (free alcohol) Merck, corticotropin peptide (Li) hydrocortisone (free alcohol) Upjohn and a highly concentrated adrenocortical extract by Upjohn For many months the hormone used was chosen not according to its particular suitability or the physician s preference but because of its availability In 1949 and 1950 corticotropin was more readily available than was cortisone When supplies of cortisone acetate for intramuscular use became more plentiful reports on cortisone increased

During the four years 1950–1953 other preparations were made Those available commercially have been cortisone acetate tablets for oral use hydrocortisone (free alcohol) in tablet form for oral use hydrocortisone acetate in suspension for intrabursal and intra articular use and a long acting corticotropin Those available for research purposes have been corticotropin peptides tablets of cortisone (free alcohol) pellets of cortisone and solutions

Table 8

COMPARISONS BETWEEN CORTISONE OR HYDROCORTISONE AND CORTICOTROPIN WITH SPECIAL REFERENCE TO THEIR EFFECTS IN RHEUMATOID ARTHRITIS

	Cortisone and Hydrocortisone	*Corticotropin*
Physical state	Crystalline steroid	Protein polypeptide
Standardized potency of preparations	Constant*	Variable
Physiologic potency	In general—equal	
Relative potency of dosage	2–4 (av 2 5) mg of cortisone produces same clinical effect as 1 unit of corticotropin given intramuscularly Hence 100 mg of cortisone = 40 ± units of corticotropin	
Antirheumatic potency	In general—equal	
Site of action	On end-organ the cell level*	Only on responsive adrenal cortex
Routes of administration Oral	Active* Maximal clinical effect of single dose in 4–8 hr	Inactive
Intramuscular	Slow effect 12–24 hr Only 1–2 daily doses required Maximal effect in 8–12 hr	Regular preparation—rapid effect 6 8 hr maximal clinical effect 4–6 hr 2–4 daily doses required Long acting preparation—slow effect 12–24+ hr 1–2 daily doses required
Intravenous Onset of effect	Rapid	Rapid
Duration of effect	Fairly short	Prolonged
Local joints bursas eyes	Effective	Ineffective
Contamination	None	Minimal (posterior and intermediary pituitary substance)
Sensitivity anaphylactic reaction	Rare or absent nonantigenic*	Occasionally antigenic
Refractoriness gradual diminution of antirheumatic effect	Occasional (?)	Earlier preparations—common Newer preparations—less common

* See Over all usefulness in last lines of Table 8 on next page

Table 8—(Continued)

	Cortisone and Hydrocortisone	*Corticotropin*
Effect upon adrenal cortex		
Histology	Atrophy (reversible)	Hypertrophy (reversible)
Function	Depressed	Increased if adrenal responsive
Posthormonal adrenocortical insufficiency	May be notable if withdrawal is rapid	Less notable (?)
Effect upon anterior pituitary		
Histology	Altered (reversible)	
Function	Secretion of endogenous corticotropin inhibited	
Production of undesirable physiologic effects = side effects	In general—comparable	
In presence of contraindications		
Hypertension	Preferred	
Edema	Preferred	
Cardiorenal	Preferred	
Nitrogen loss before treatment		Preferred
Over all usefulness in chronic rheumatic diseases	Generally preferred because of points starred (*) on preceding page	Valuable for special uses

of cortisone hydrocortisone and corticotropin for intravenous use After tablets of cortisone acetate became generally available in December 1950 the reports on cortisone especially its long term use in rheumatoid arthritis increased Now reports on hydrocortisone are increasing

The similarities and the important differences in the physiologic clinical and other effects of cortisone or hydrocortisone and corticotropin are outlined in Table 8 [5 9 16 9 30 67–83]

Patients Selected For our first study the patients selected had severe inflammation and disability but intra articular destruction was not marked the disease was reversible not hopeless The results obtained showed the propriety of such a choice Although the hormones greatly influenced the reversible aspects of rheumatoid arthritis they exerted no influence on its irreversible effects

Subsequently other physicians used the same criteria for a time but when hormonal supplies increased this careful limited selection was aban

doned Patients treated have included young children and adults of all ages [69–92] The disease was mild or moderate in some, severe in most of the cases reported [71 79 80 93–96] Although some patients had had minimal treatment prior to the use of hormones, most of them had received "almost everything" analgesics physical therapy, diets, vitamins gold salts (either without relief or with toxic reactions), copper and orthopedic measures

Many of the cases reported to date have been unsuitable for treatment with hormones if not hopeless, because of a predominance of irreversible changes But it is understandable that physicians treated their most severely affected patients and that the latter wanted to have their chances for limited relief The severe testing (some workers have called it an impossible testing) which the hormones have received has demonstrated clearly their limitations as well as their unprecedented antirheumatic potency

Examination of Patients before and during Treatment Earlier patients were subjected to many examinations and laboratory procedures before, during and after treatment These were made to discover contraindications to determine adrenocortical responsiveness to corticotropin to measure progress to control or prevent undesirable reactions and to uncover the mechanism of hormonal action Through them were determined the biochemical and metabolic disturbances which characterize hypercortisonism (see later discussion of hypercortisonism on page 213) and the boundaries of safe dosage But experience disclosed that treatment could be controlled by careful clinical supervision aided by a few simple tests

General Results Irrespective of Choice of Hormone Dosage or Duration of Treatment

Characteristic Response *Clinical* The general pattern of clinical improvement as first described[6] has proved to be characteristic [24 89 97–101] Lessening of subjective symptoms begins usually within two or three days, sometimes within a few hours after the first doses of cortisone, hydrocortisone or corticotropin Within a few days muscular and articular stiffness aching and pain on motion and articular tenderness and swelling usually decrease As treatment is continued thereafter further improvement is more gradual sometimes being interrupted by minor flares The maximal over all improvement occasionally develops after a few or several months' treatment

Patients commonly note increased strength lessened toxemia improved appetite with gain in weight and increased mental and physical vigor Fever if present commonly disappears Rheumatoid nodules and enlarged lymph nodes sometimes diminish in size or disappear Enlarged spleens may diminish in size Flexion contractures if moderate and of fairly recent duration, may disappear during treatment if of long standing they are unaffected or lessen only slightly

Biochemical and Metabolic Erythrocyte sedimentation rates (E S R s) are usually reduced Concentrations of hemoglobin and erythrocyte counts of anemic arthritics often increase Total leukocyte counts usually increase

Eosinophil counts are commonly reduced notably by corticotropin but are not affected consistently by cortisone When hyperglobulinemia is present reduction of serum globulin usually occurs and albumin globulin ratios tend to return to normal Urinary corticosteroids are increased by cortisone or corticotropin Urinary 17 ketosteroids are increased by corticotropin variably affected by cortisone

Significant alterations in the concentrations of electrolytes in blood or tissue are usually not produced (within the first few weeks at least) by small or moderately large daily doses cortisone 100 mg or less in men 75 mg or less in women corticotropin 30 to 40 mg or less in men 25 to 30 mg or less in women But such doses given persistently or larger doses often produce an increased excretion of potassium and chloride with a resultant hypopotassemic hypochloremic alkalosis

General Effectiveness As antirheumatic agents the hormones were considered unique in their dependability speed of action, and effectiveness Results were commonly described as marked or dramatic [101–103] Practically all patients with active but reversible disease developed marked relief [10–106] The percentage of patients with active disease who have been completely unresponsive to the doses generally used has been about 2 or 3 per cent Results were less striking among patients with severe disability and little or no inflammatory activity

Factors Modifying General Results The patient s age sex or weight of themselves had no influence on results Patients of all ages responded well and women who tolerated effective doses responded as well as men [64, 107] But fewer women can tolerate the more effective doses Lessened tolerance though statistically greater among females may be related to some physiologic difference which may not be as unisexual as now appears Menopausal or postmenopausal women tend to have a lower tolerance to the hormones than those who still menstruate regularly [9, 64]

There is no direct relationship between hormonal effectiveness and the duration of the disease when the latter is considered per se i e results have been about the same in cases still considered mild after many years as in mild cases of recent onset [85, 107, 108]

The term *severity of disease* means the intensity or severity of the active inflammation which is reversible and not the amount or severity of the crippling deformities which are irreversible The two are often confused Disregarding momentarily the important matter of tolerance the severity of the rheumatic inflammation does not per se influence results [108] The most dramatic results have occurred in severe cases given enough hormone the most severely affected patient usually responds a remarkable demonstration of potency But from the standpoint of practical therapeutics the severity of the disease exerts a most decisive influence because it more than any other known factor governs the dosage required for full clinical effect As a rule the more active the disease the higher must be the early suppressive doses generally but not always this is also true of the later follow up or maintenance doses [9, 61, 80, 100, 108–111] Rheumatoid patients with disease severe

enough to require high doses usually find them to be effective even tolerable for awhile but not indefinitely

Results were often reported without separating duration and severity Thus to different writers an "old severe case" meant *(a) one in which years* after the onset of the disease severe inflammation was present but not necessarily severe deformities *(b)* one of long-standing with marked crippling but little or no active inflammation or *(c)* a case with both severe inflammation and deformities Severity and duration of disease, combined with deformities, have been found to lessen notably but not to exclude entirely the chances of a worth while result [9 80 90 10 105 11]

Severe cachexia reportedly abolishes the effectiveness of cortisone or *corticotropin* [96 113]

The Patient's Variable Responsiveness Notable variations in the responsiveness of rheumatoid patients to well tolerated doses of cortisone or corticotropin were reported A given dose of a potent hormone elicited a different response in different patients or in the same patient from time to time even when the disease's severity seemed to be constant This variable responsiveness was multiphasic Thus one patient's biochemical abnormalities were improved more than his symptoms Other patients obtained marked relief without changes in the E S R circulating eosinophils or urinary steroids[114] remained essentially unchanged

Kellgren Janus and their associates[115–117] studied the responsiveness of rheumatoid patients to single doses and three-day courses of cortisone or corticotropin A given dose of either hormone produced not only 'full symptomatic relief' but also *signs of hypercortisonism in some* patients, no effect of any sort was observed in others

Many factors may influence responsiveness to either hormone e g rates of hormonal absorption or destruction degree of tissue responsiveness amount of tissue requirement and the level of endogenous corticosteroids at the time the exogenous counterpart is given [101 118]

Special Clinicopathologic Effects

Ocular Lesions in Rheumatoid Arthritis Systemic or topical therapy with hormones has given excellent results in rheumatoid cases with acute plastic[119 120] or nongranulomatous iritis,[1 1] acute fibrinous iridocyclitis [79 1 2 123] keratoconjunctivitis [79] scleritis and episcleritis [1 1 4 1 5] Inflammations of the anterior segment of the eye have commonly responded well to topical therapy with cortisone or hydrocortisone in eye drops or ophthalmic ointment Results from hydrocortisone equaled or surpassed those from cortisone [126] Inflammation of the posterior segment generally required systemic treatment [123] Occasionally a previously unaffected eye would participate in a relapse on withdrawal of the hormone [1 7]

Two patients with moderately advanced Sjogren's syndrome[1 8] did not respond to a short course (500 mg) of corticotropin But another patient with rheumatoid arthritis dry eyes and dry mucous membranes had tears and saliva after treatment for nine days with corticotropin [99] One case

reportedly responded to hypophyseal implantation [129] Multiple scleral nodules of 2 patients with rheumatoid arthritis and scleromalacia perforans diminished or disappeared during the intramuscular use of cortisone These nodules were histologically identical with the subcutaneous rheumatoid nodules also present in 1 case Involutionary histologic changes developed in 1 case but in the other the histologic picture changed little if at all [130–13] The results obtained by Quinn and Wolfson [133] who gave unusually large doses of long acting corticotropin for from 13 to 220 days to 33 nonrheumatic patients with ocular diseases are discussed at length in Chapter 11

Synovial Membranes Biopsies of synovial tissues, usually of the knees before during and after use of cortisone or corticotropin disclosed reduction of synovial inflammation by the hormones Histologic improvement was mild moderate or marked depending upon the length of time the hormones were given and upon the patient s response The synovial tissues though almost always improved were not fully restored to normal [9 134] Improvement *consisted of reduction of the cellular reaction with decreased numbers* of plasma cells and lymphocytes reduction of papillary tufting reduction or absence of deposits of fibrin lessened edema and evidence of fibrous healing Such improvements resemble those which occur during spontaneous remissions [13 136] Repeated synovial studies can now be made conveniently by punch biopsies[137–140] despite some limitations

Subcutaneous Nodules During treatment subcutaneous juxta articular nodules have become less tender softer and smaller (sometimes appreciably smaller) and sometimes fragmented [9] Small or recent nodules have occasionally disappeared completely [9 7 102 111 115 130 13 141–145] They have been seen to become smaller during each course and larger between courses of treatment [10]

Whole nodules or halves of nodules have been removed before treatment and compared with others removed during or after treatment Observed results have varied [9 111 115 14 144] but according to two comprehensive studies the following occurred Spontaneous involutionary changes commonly developed in nodules of untreated patients These were accelerated by the hormones which hasten regression by preventing the occurrence of further activity [130] The central necrotic zone became poorly defined The surrounding layer of large mononuclear cells in palisade formation sometimes practically disappeared The outer zone of connective tissue became more dense or hyalinized and its characteristic round cell infiltration markedly diminished [143]

Lymph Nodes Enlarged lymph nodes have diminished in size during use of cortisone[9] or corticotropin [27 89 146]

Intramuscular Inflammatory Lesions These characteristic but non pathognomonic lesions present in more than half of rheumatoid patients [147] consist of inflammatory micronodular collections of lymphocytes and of degenerative lesions In patients given cortisone or corticotropin inflammatory nodules disappeared or decreased degenerative lesions improved to a lesser extent [143]

enough to require high doses usually find them to be effective, even tolerable for awhile but not indefinitely

Results were often reported without separating duration and severity Thus to different writers an "old severe case" meant (*a*) one in which years after the onset of the disease *severe inflammation was present but not* necessarily severe deformities (*b*) one of long standing with marked crippling but little or no active inflammation, or (*c*) a case with both severe inflammation and deformities Severity and duration of disease, combined with deformities have been found to lessen notably, but not to exclude entirely, *the chances of a worth while* result [9 80 90 10 105 11]

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Table 9

ADRENAL WEIGHTS OF NORMALS, RHEUMATOID AND NONRHEUMATOID PATIENTS WITH AND WITHOUT HORMONAL TREATMENT

Classification		Cases Studied	Weight of Paired Adrenal Glands (Gm.)		References
			Average	Range	
Normal (control)	Age (yrs.)				
	Birth		7.9		159
			9.0		160
	1		4.7		
	2		5.8		
	3½		6.9		161
	5		8.0		
	11		9.3		
	20		11.6		160
Adults (traumatic death)		50	8.3	5.8–11.3	16
Adults (traumatic death)		12	9.35	6.1–13.5	163
Nonrheumatic adult patients					
No hormones		65	11.0	6.4–18.4	163
No hormones		42	12.6 ± 0.5	8.0–19.2	164
Corticotropin		8	18.0	8.4–32.0	*
Cortisone		46	9.8 ± 0.4	5.9–16.8	164
Adult rheumatoid patients					
No hormones					
Corticotropin alone		1		35.0	62
First cortisone, then corticotropin		1		23.4	147
Cortisone alone		6	10.2	5.6–21.0	†
First corticotropin, then cortisone		2	12.7	9.4–16.0	163

* Our cases 1950–1951
† Our cases 1950–1953

cytologic destruction attributed to a holocrine type of response precipitated by the combination of hormonal agents.[167] However, no such cytolysis was found in many other patients given first one hormone, then the other.[113, 155, 157, 168]

Cortisone and Corticotropin Given Concurrently. The morphologic effect of cortisone upon the adrenals of animals can be prevented or counteracted by the concurrent use of corticotropin,[169, 170] but no morphologic data pertinent to this consideration are available in human beings as yet.

Comment. Because material is limited, current opinion is tentative; furthermore, most observers have not differentiated the hormonal responses of the adrenals and pituitaries of rheumatoid patients from those of nonrheumatoid patients.

Many factors govern development of morphologic changes. Of most obvious importance are total dose and duration of treatment. In general, fairly large amounts of cortisone (2,000 mg. or more) are required to produce significant atrophy of either gland,[163] but individual responsiveness causes

Spleen Splenomegaly decreased in certain cases of Felty's syndrome [148, 149]

Effects of Cortisone and Corticotropin upon the Morphology of Pituitary and Adrenal Glands in Rheumatoid Arthritis

Until recently little attention has been paid to the pituitary and adrenal glands of rheumatoid patients at necropsy Consequently little is known about the morphology of these glands in rheumatoid patients who have not been treated with hormones except that in routine studies no significant changes have been reported [150–15] Of special interest therefore is the report of Pearse [153] who found in each of 9 cases of rheumatoid arthritis a specific change in the mucoid cells (basophils cyanophils) of the pituitary which is closely related to the changes seen in Addison's disease'

The current widespread use of cortisone and corticotropin has stimulated an interest in the effects of these hormones upon the various endocrine glands and studies have revealed that if enough of either hormone is given changes in weight cytology cellular chemistry, and function occur in the anterior pituitary and the adrenal cortices

Pituitary Body Administration of cortisone or corticotropin or both has resulted in the appearance of Crooke's hyaline changes in the basophilic cells of the anterior pituitary in many nonrheumatoid patients [154–159] Similar changes have been reported in rheumatoid patients treated with cortisone alone or with cortisone and corticotropin given alternately [154, 155, 157] although to date there appears to be no report on pituitaries of rheumatoid patients given corticotropin alone Resistance of the pituitary cells to hyalinization occurred in a higher percentage of cases of rheumatoid arthritis than in other cases in one series [154, 155, 157] There was a general correlation between the cellular alterations and the total dose However the changes are reversible hence the greater the interval between the last dose of hormone and death the more nearly normal the pituitary cells appeared But the speed of both production and reversibility varied in different persons [154, 155, 157]

Adrenal Glands Administration of either cortisone or corticotropin produces similar alterations in the pituitary However the two hormones have different effects upon the adrenal glands (Table 9)

Cortisone Cortisone produces reversible cellular atrophy and depletion of lipid material in the fascicular and reticular zones of the cortex although the glomerular zone is commonly well preserved These changes have been noted in both rheumatoid and nonrheumatoid patients [113, 154, 155, 157, 163–166]

Corticotropin Corticotropin produces reversible hypertrophy and hyperplasia and reduction of lipids in all three zones of the cortex at least in nonrheumatoid patients [163, 16] No data appear to have been published on detailed morphologic changes in the adrenals of rheumatoid patients who received corticotropin alone

Cortisone and Corticotropin Used Alternately The administration of cortisone was followed by corticotropin in a case of lupus erythematosus Adrenals were small and thin and in the fascicular zone there was marked

atrophy by cortisone (3) Adrenocortical response to stress as measured in experimental animals by adrenocortical hypertrophy and depletion of ascorbic acid and cholesterol in the adrenal cortex is blocked by the administration of cortisone (4) Cortisone does not cause further reduction of adrenal weight in hypophysectomized rats (5) The histologic appearance of the adrenal cortex in rats treated with cortisone is similar to that of hypophysectomized rats (6) Morphologic changes in the anterior pituitary are similar after administration of cortisone and corticotropin [164, 170–177] It is possible however, that cortisone also exerts a direct effect upon the adrenal cortex [171]

It is well recognized that the primary action of corticotropin is to stimulate the function of the adrenal cortex [171] However administration of corticotropin also suppresses the corticotropic function of the pituitary probably because it causes the production of increased levels of adrenocortical steroids When treatment with corticotropin is stopped this suppression of corticotropic function results in temporary adrenocortical insufficiency as indicated by weakness fatigability hypotension decreased urinary excretion of 17 ketosteroids and corticosteroids and relative increase in eosinophils on withdrawal of corticotropin [171]

Thus the effects of cortisone and corticotropin on the adrenal cortex differ during administration Cortisone suppresses but corticotropin stimulates adrenocortical function However, both hormones suppress corticotropic function of the pituitary As a result temporary inhibition of the corticotropic adrenocortical function and potential adrenocortical insufficiency may occur on cessation of prolonged treament with either hormone

The period of administration of hormones necessary to produce corticotropic adrenocortical suppression is not predictable there is evidence that administration of cortisone for only five days may cause suppression in some instances [164] The severity and duration of the clinical evidences of suppression vary considerably from patient to patient but ordinarily the reaction has been most marked in those who have been treated for more than two months [178] Following prolonged treatment for several months or more corticotropic adrenocortical suppression may persist up to three months rarely longer [85, 109, 164, 171, 179] The relation of dosage to the severity and duration of the suppression has not been completely defined Our clinical impression is that the reaction has been more severe and prolonged if the doses employed produced obvious clinical evidences of hypercortisonism Theoretically any dose equal to or exceeding the daily physiologic requirement (a quantity not yet precisely determined) may suppress endogenous function [164]

Two Basic Plans of Hormonal Administration in Rheumatoid Arthritis

From the standpoint of length of hormonal administration there are two basic plans but the physician may interchange them and temporarily substitute one for the other at any time

much variation Thus in 1 case some cortical atrophy was noted after administration of 400 mg of cortisone in 4 days,[155 157] whereas in another in which cortisone was given daily for 287 days, the adrenals appeared to be small but within the limits of normal [95 113] The duration of treatment is as important as, if not more important than total dosage

In no case (unless hormones were actually responsible for the cytolysis in the case of Proctor and Rawson[167]) have the hormones altered the fundamental architecture of the adrenal cortex Morphologic changes are reversible "despite the use of enormous doses over a period of many months,"[163] although histologic repair may develop rapidly in some cases tardily in others No definite statements have been made concerning the speed or degree of reversibility (1) as between pituitary and adrenal responses to the same hormone, or (2) as between the effects of cortisone and those of corticotropin upon either gland

Both the pituitary and adrenal changes are secondary and compensatory in nature the prime factor in both cases being the increased concentration of circulating adrenocortical steroids

Finally, glandular form and function are two different matters and either restoration or degeneration of cells as visualized microscopically may develop at a speed different from that of alterations of function Also a gland s basal function and its reserve function are two different matters Therefore in attempting to relate these important data to the field of practical therapeutics it must be realized that maintenance or recovery of glandular form does not necessarily indicate recovery of normal function and that a gland s reserve function is not necessarily normal or adequate for stressful situations even though its basal function is clinically adequate

Effects of Cortisone and Corticotropin upon Function of the Pituitary and Adrenal Cortex

Administration of cortisone temporarily suppresses adrenocortical function as evidenced by (1) decreased urinary excretion of 17 ketosteroids during administration of cortisone (50 to 75 mg) (2) clinical manifestations of adrenal insufficiency (weakness fatigability and hypotension) on withdrawal of cortisone (3) decreased urinary excretion of 17 ketosteroids and corticosteroids and increase in eosinophils when administration of cortisone is stopped (4) decreased ability of adrenal cortex to respond to corticotropin after administration of cortisone as measured by excretion of 17 ketosteroids or corticosteroids response of eosinophils or clinical response (5) morphologic evidence of adrenocortical atrophy following administration of cortisone [35 113 147 155 157 163–165 171]

However, certain observations suggest that temporary adrenocortical insufficiency on withdrawal of cortisone is largely a result of the suppression by cortisone of the corticotropic function of the anterior pituitary (1) Decreased serum levels of corticotropin follow administration of cortisone (2) Administration of corticotropin prevents the production of adrenocortical

hormone are the standard procedure Although cortisone tablets are convenient, corticotropin may be employed A course of treatment commonly is comprised of three phases or dose periods for (1) suppressive doses (2) steplike reductions in doses and (3) maintenance doses

Cortisone For a short time a priming dose of 300 mg was used, then suppressive doses of 100 mg Recently the trend has been toward initial doses of less than 100 mg for only a few days and slow reduction throughout the course [9, 49, 95, 103, 111, 180–18]

Hydrocortisone Though equally appropriate for short term or course treatment hydrocortisone has been used mostly for prolonged treatment

Corticotropin Early suppressive doses were high 40 to 100 mg daily then reduced[65, 180] about 50 per cent Recently suppressive doses usually have been 40 units or less daily with correspondingly smaller doses thereafter

Length of Courses Cortisone and corticotropin were given variously for one to eight weeks (total dosage 3 to 4 Gm) [65, 90, 97–107] Wide differences of opinion as to the optimal length of a course still persist, recently recommended were courses averaging from 10 days[79] to 8 months [183]

Length of Rest Periods Rest periods sometimes lasted two to six weeks Length of most rest periods despite their name and supposed purpose has been governed by the return of rheumatic symptoms and not by tests indicating normalization of adrenocortical and pituitary function

Such fixed courses and rest periods often failed to provide optimal results Therefore as familiarity with the use and the effects of the hormones increased the courses were usually lengthened and the rest periods shortened to the extent that now the latter usually are tests of articular rather than of glandular function At the Mayo Clinic the doses used and the length of each course and of the intervening period have been determined by each patient s response because no one optimal course for general application has been developed [61, 184]

General Results of Short-Term Administration *During Any Single Course* Representative general results from short term or course treatment given in Table 10 are presented without reference to total dosages or length of cour es Classifications of results were not always comparable but results were grouped as closely as possible

The differences between the results in our first series of cases[9] and the later results of others are of interest Doses were higher and courses were usually longer in our cases than in those of others [79, 99, 100, 108, 155, 186] Therefore our patients obtained more nearly complete relief but also more disturbing undesirable effects in other words maximal rather than optimal relief Nevertheless optimal doses or do es for optimal effect are safer and more practicable than maximal doses Courses of a few weeks of treatment produced relatively few significant side effects [101–106]

Cortisone and corticotropin were considered equally effective by those who gave comparable doses and courses of each to the same patients[79] or who spoke in general terms [103] Among cases first reported symptomatic

Plan 1 Interrupted or Short-Term Administration

Plan 1 provides interrupted administration repeated courses of one or the other hormone each limited to a few weeks or months and followed by a rest period (without any hormone) that usually lasts until enough symptoms return to warrant using the hormone again The purpose is to give temporary, optimal—or in selected cases, maximal—relief, the hormones being either the major remedy for a limited time or supplemental to special treatment such as corrective physical therapy or orthopedic procedures

Advantages are these Undesired effects are minimized major ones are rare The cost of treatment is lessened unless relapses are severe and prompt During rest periods adrenocortical and pituitary histology and function tend to normalize and one can see whether further treatment is required or whether a significant remission has developed, the latter may occur in about 10 per cent of cases

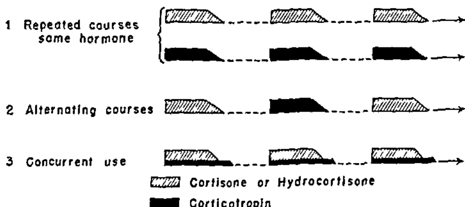


Fig 22 Variations of Plan 1 the course method

Disadvantages are the relapses which usually develop between courses the limited ability of patients to readjust to a return of their disease and, if discontinuance has not been done properly the withdrawal reactions

Plan 1 has lost favor during the past year or two but it is still recommended by certain workers[106] We consider that Plan 1 is indicated for rheumatoid patients (1) whose disease is episodic and characterized by therapeutic or spontaneous remissions (2) who are relatively intolerant of usual hormonal doses (3) who need large doses which if long continued would cause undesired effects that cannot be well controlled, (4) who have conditions, such as peptic ulcer diabetes mellitus or nephritis which are relative contraindications to hormonal therapy (5) who need one or more courses to supplement physical therapy or orthopedic procedures or (6) who are concerned about long term treatment

Programs for Plan 1 Courses are individualized Several factors are involved choice of hormone general level of early and also later dose rate of reduction, length of course and the length of time between courses Several variants are shown in Figure 22 Repeated courses of the same

did develop to a given animal species of corticotropin sometimes necessitating a change to a different type

Variants of Standard Plan 1 Various modifications of the standard plan have been tried in hopes of finding a superior scheme namely (1) a quick on again–off again use of cortisone[9, 10] e g cortisone for two to seven days with treatment free intervals of three to seven days (2) large doses (100 mg of cortisone daily) for a few days alternating with smaller doses (50 to 75 mg daily) for a few days and so on[10] (3) high doses (150 to 200 mg of cortisone intramuscularly) on alternate days only[102, 185] (4) repeated courses of cortisone—some tapered some not—with a variant given to see whether the adrenal cortex might improve or quicken its accommodation to discontinuance of treatment[9] (5) a short course of very high or excessive doses[189–191] (6) alternating courses of cortisone and of corticotropin with intervals between courses and (7) repeated short courses during each of which both cortisone and corticotropin were given daily[61, 19, 193] These modifications have usually given disappointing results The sixth and seventh may deserve further trial

Supplemental Use of Plan 1 Short courses of cortisone or corticotropin have been useful in controlling acute exacerbations when everything else fails also as adjuncts to corrective physical therapy manipulation and other orthopedic measures for the correction of deformity[80, 89, 96, 186, 194–198]

Short-Term Use of Special Hormonal Preparations ***Cortisone Pellets Implanted Subcutaneously*** A few rheumatoid patients received implantation of pellets of cortisone results if any were of short duration[181, 199]

Corticotropin Given Intravenously A dose of corticotropin given intravenously by slow infusion is much more effective than a similar quantity given intramuscularly[00, 01] Continuous 24 hour infusion provides a maximal effect but is impractical for routine use because of discomfort venous thrombosis or cellulitis which may occur[0] But 8-hour infusions of 10 to 20 U S P units (dissolved in 500 to 1 000 cc of 5 per cent solution of dextrose in distilled water or saline solution[187, 03]) are useful and have the therapeutic effect of 100 to 150 units of lyophilized corticotropin[171] Such infusions are indicated (1) when large intramuscular doses of corticotropin are inadequate (2) to combat resistance to corticotropin given intramuscularly and (3) to reactivate quickly cortisone inhibited adrenals[113, 01, 04, 05]

Anaphylactic reactions have rarely *developed in patients with normal* adrenal function but patients should be watched closely during the first 20 minutes of infusion[06] Patients may note early warmth sweating and flushing of skin[01, 20] Resistance to corticotropin given intravenously does not develop even when resistance to the same animal species of corticotropin given intramuscularly had previously occurred[06]

Undesirable effects have been qualitatively the same as those from intramuscularly administered corticotropin but they may appear earlier because of the enhanced effect Therefore dosages must be watched carefully and low salt diets (2 Gm daily) and potassium chloride (1 8 to 5 4 Gm daily) should be prescribed if intravenous treatment is given for more than

Table 10

SHORT TERM USE OF CORTISONE OR CORTICOTROPIN IN RHEUMATOID ARTHRITIS—RESULT OF COURSE TREATMENT (PLAN 1) REPRESENTATIVE REPORTS

Workers	*Hormone Used*	*Patients Treated*	*Relief (Percentage of patients treated)*			*Mild Fair or Poor Results (Per cent)*
			*More or Less Complete**	*Marked†*	*Moderate‡*	
Hench and co workers[9]	Cortisone§	21	57	38	5	
Hench and co workers[9]	Corticotropin§	6	67	33		
Total—Maximal Doses		27	59 (16 patients)	37 (10 patients)	4 (1 patient)	
Bilka[165, 186] Holbrook and co workers[99] Fischer and Gillmor[79]	Cortisone	131	12	66	12	10
Rosenberg and co workers[108] Fischer and Gillmor[79]	Corticotropin	79	2	61	32	5
Steinbrocker and co workers[100]	Cortisone and Corticotropin (Results not separated)	72	4	40	54	2
Total—Optimal Doses		282	7	58	28	7

* 90 to 95 per cent relief of symptoms
† 75 to 90 per cent relief of symptoms
‡ 50 to 75 per cent relief of symptoms or Stage II of Steinbrocker's [100] classification
§ Doses were larger and courses were often longer in this early series of cases than in the others hence these results are not included in the totals given in the last line

relief was sometimes greater from corticotropin than from cortisone because corticotropin's greater potency by weight was not yet clearly appreciated and the doses of corticotropin were physiologically larger than those of cortisone [9, 79, 113, 116, 187, 188] Because of individual responsiveness certain patients have obtained better (occasionally much better) results from one or another of the hormones

During Subsequent Courses of the Same Hormone A later course or subsequent courses of the same hormone usually produced results similar to those obtained initially Refractoriness did not develop to cortisone but

Policies of Dosage Although most physicians agree on the general policies there is no agreement with regard to the best general level of dosage Actually almost all physicians subscribe to the same over all policy on dosage give enough to provide noteworthy relief without significant undesired effects But in practice they differ in their concept of the dose required to accomplish this Physicians are divided among those who consider that rather high doses are usually required those who consider that lower doses somewhat closer to the physiologic are commonly effective and those who generally use doses somewhere in between [52 69 109 96 21]

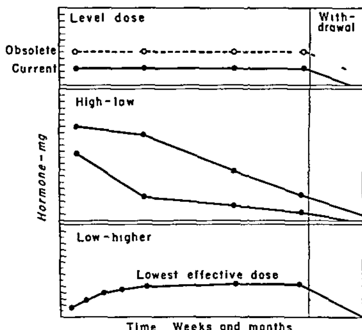


Fig 23 Three main dosage programs for prolonged hormonal therapy level dosage falling high low dosage and a rising low higher dosage The first high level pattern (broken line) e g cortisone 100 mg daily indefinitely as first used is obsolete but a low level pattern (solid line) is used currently in selected cases Two variants of the falling high low pattern are currently used one involving larger pharmacologic doses and one involving smaller paraphysiologic doses In the rising low higher pattern small possibly ineffective test doses are given first then increased gradually to the lowest effective dose

Schemes of Dosage The prolonged hormonal treatment of rheumatoid arthritis would be greatly simplified if one superior scheme of dosage could be devised Instead the process of individualization has resulted in the establishment of many schemes The physician, then has a choice and can tailor the scheme to any given patient

Components of a Dosage Scheme The components of a dosage scheme include the over all direction of dosage or changes in doses (Figure 23) whether (1) more or less level (2) in general down gradually or rapidly or (3) gradually up at least for a while If the second type is selected there is

two days [91] Despite intense adrenocortical activation, adrenals became hypoactive within one or two days after such therapy was stopped Renold and associates [91] gave an eight hour infusion on the second and fifth days after the last of the daily infusions to prevent withdrawal reactions

Long Acting Corticotropin [83 207-09] The duration of a satisfactory clinical effect from early preparations (Adactar Armour) was variable amounting to 24 hours in some cases but usually less [207] The efficiency of a given 24 hour dose was only about 70 per cent of that of an equal dose of the aqueous solution given every 6 hours in divided doses An injection of corticotropin gel once a day has satisfied patients whose daily requirement was small But when patients needed a total of 30 to 40 units daily two injections each day have usually been required Improved preparations have been made but their usefulness for rheumatoid patients has not been reported [171]

Corticotropin Peptides Several corticotropin peptides have been active physiologically, but they are not available commercially Clinical and metabolic effects were like those from corticotropin protein [34 91 117 10 11]

Plan 2 Continuous or Prolonged Hormonal Administration

This plan involves the prolonged use of one or another of the hormones more or less continuously usually for as long as the disease is active and can be suppressed satisfactorily by well tolerated doses Its purpose is to provide as much relief for as long as possible without significant adverse effects When satisfactorily applied it prevents the relapses psychologic readjustments and withdrawal reactions characteristic of Plan 1

Its disadvantages are (1) the limited tolerance of some patients to indefinite use of worth while doses (2) increased liability to undesired effects if relatively high maintenance doses are required, (3) cost of continued medication and of medical supervision needed for an optimal result and (4) masking or delayed recognition of a spontaneous remission (should one develop during prolonged therapy) if hormonal withdrawal is not attempted every so often

Offering hope of prolonged relief this plan has a strong appeal to many rheumatologists and patients It has been made feasible by the introduction of cortisone or hydrocortisone tablets and of long acting corticotropin Prolonged administration involves more of a calculated risk than the course treatment But its disadvantages have been lessened considerably by time and experience

General Policies of Prolonged Treatment To test the disease s activity and the patient s continuing need for treatment most physicians favor gradual discontinuance of treatment routinely either at predetermined intervals or at some indeterminate time when symptoms remain in abeyance despite progressive dose reductions Most physicians state that not maximal, but submaximal or optimal relief is the goal i e relief of about 75 to 80 per cent of symptoms or to the extent that the patient can work or live in reasonable comfort probably using older treatments as supplements But a few believe that with careful supervision maximal relief may be attempted [33]

a period (1) for 'priming doses' (one to three days) (2) for suppressive doses (3) for dose reductions and (4) for maintenance doses with several factors to be considered in each period The size of the first suppressive dose must be determined whether high medium high or medium, and the duration of the period of suppressive doses This involves deciding on the length of time the fixed suppressive dose is to be used before dose reductions are begun, or if graduated suppressive doses are used, the length of time before maintenance doses are reached

In the dose reduction period the components are (a) the general size of each dose change which if all goes well is a decrement but sometimes is a temporary increment or booster dose (b) the length of time each new dose is used before the next change is made (c) the over all duration of the period of dose reductions until maintenance doses are used In the maintenance dose period factors to be determined are (1) the size of the first dose which the physician regards as a maintenance dose, (2) the length of time spent in reducing the maintenance dose to zero and (3) the size of the increments or decrements used in making any necessary adjustments in the maintenance dose Since any one or several of these factors vary from case to case a dosage scheme constitutes a rather complex formula an individual hormonal prescription No two rheumatoid patients are likely to have had the same formula

Variants of the Dosage Scheme Reviewing the developmental changes that have been made in dosage schemes since 1948 one finds 11 different patterns (Figure 24) consisting of 8 variants of the high low program 2 variants of the level dose program and 1 low higher program In general each variant was designed to correct some fault in an earlier scheme or to

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obsolete in our opinion Pattern 5 is obsolescent although it is often employed Patterns 6 to 11 are in current use Among our group the following are employed most frequently Patterns 6 7 and 10 an individualized version of Pattern 6 for severe arthritis Pattern 7 for most patients and Pattern 10 or 11 for patients with mild or moderate inflammation superimposed on old irreversible changes

Pattern 1 The high level pattern—prolonged (six to nine months) administration of a high or fully suppressive dose *Pattern 2* A high or full dose given for several to many weeks then a half dose This was the first high low program *Pattern 3* A high priming dose for one day thereafter Pattern 2 *Pattern 4* A full suppressive dose daily for several weeks until maximal clinical effect is obtained next graduated reductions of dose then a relatively fixed maintenance dose *Pattern 5* A high priming dose for one to three days then a full suppressive dose (generally 100 mg daily) for about two to five weeks thereafter graduated reductions of dose to maintenance doses *Pattern 6* A full suppressive dose for only one to two weeks otherwise similar to Pattern 4 *Pattern 7* The flexible pattern with the length and dosage individualized and made flexible throughout graduated reductions of the individualized suppressive dose from the very beginning no fixed suppressive dose no semifixed maintenance dose (Figure 25) *Pattern 8* Coadministration of corticotropin injected intramuscularly and cortisone given by mouth *Pattern 9* First a moderately high test dose next an early booster dose then a graduated maintenance dose *Pattern 10* The low level pattern the modern version of Pattern 1 *Pattern 11* The low higher program Early use of a low (probably ineffective) test dose then its gradual increase to the lowest effective therapeutic level

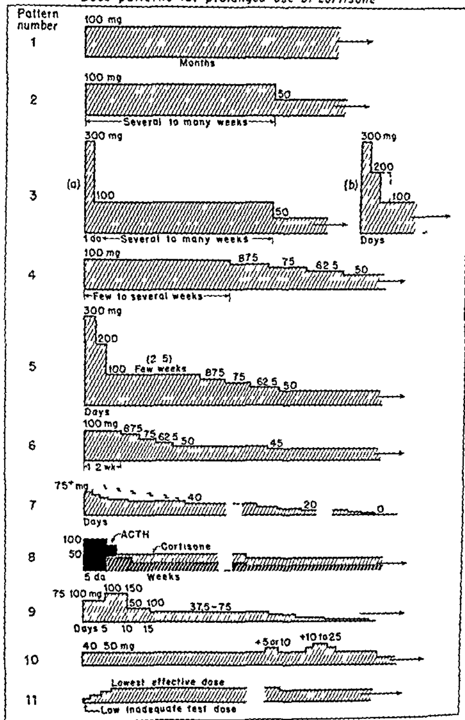


FIG 21 These dose patterns refer almost exclusively to cortisone except for combination with corticotropin (ACTH) in Pattern 8 and have not concerned hydrocortisone although the latter can be used in the same way Patterns 1 to 4 are

sive doses (about 75 mg) instead of higher ones (around 100 mg) the former being increased if necessary in some cases (5) application of the principle of dose reduction from the beginning of treatment i e during the early use of suppressive doses instead of weeks later, (6) abolition of all routine or fixed periods or fixed doses by substitution of a pattern of continuous flexibility and individualization of dosage Latest developments have been the two low-dosage schemes the low level pattern and the low higher pattern By these progressive refinements the incidence of significant hypercortisonism has been lowered without material reduction of the clinical results and the actual long term clinical result has been improved



FIG 26 Feet of a patient suitable for conservative hormonal treatment according to Dose Patterns 10 or 11 In a patient with some inflammation superimposed on irreversible destructive changes there is a tendency to keep increasing the doses beyond the realm of the practical or the possible If initial improvement is obtained the patient hopes for more and more relief but hormonal therapy cannot relieve symptoms due to mechanical stresses and old deformities This patient responded slowly but well to doses of cortisone 50 mg daily the doses then being gradually reduced over many months

Synopsis of Dosage Commonly Used in Prolonged Administration Since the various results (desirable and undesirable) reviewed here are intimately related to dosage the doses used must be reported But most physicians have gradually been adopting reduced dosages Therefore the doses mentioned even in recent references are not necessarily being used now by the workers cited

Priming doses of cortisone varied from 150 to 300 mg given intramuscularly and from 100 to 225 mg given orally doses of corticotropin ranged from 75 to 150 units given for one to three days Dose and duration depended upon the disease s severity [5 63 69 100 107 109 11 187 213–215] Although priming doses hasten muscular relief slightly they have no other helpful effect may increase the chances for hypercortisonism and should be discarded [9 75 96 180 182 215]

The suppressive dose of cortisone given intramuscularly or orally varied from 100 to 400 mg daily in severe cases [63 69 7 107 109 112 06 14 15 17] that of

suit the needs of certain rheumatoid cases Variants 1 to 4 are obsolete or not commonly used the remaining seven are all used Until recently most reports concerned Patterns 5 and 6 But these have been discarded by some workers in favor of one or another refinement (Patterns 7 to 11)

No one pattern can be applied routinely in all cases and the physician should select that which seems best for each patient For the past two years our group has been using Pattern 7 in most mild or moderately severe cases and in some severe cases in women For severe disease among men we prefer to use an individualized version of Pattern 6 but sometimes have to use Pattern 4 For old chronic disease with mild or moderate inflammation

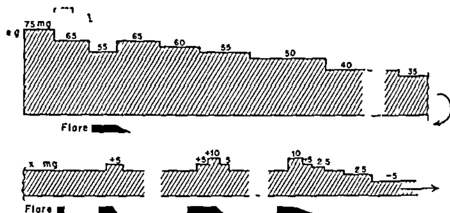


FIG 25 Pattern 7 A flexible pattern for prolonged use of cortisone or hydrocortisone with complete individualization of treatment—no fixed doses or dosage periods *Bottom section (left to right)* Daily doses for flares for minor variations of symptoms—no increment for mild flare—increment of 5 mg may suffice for moderate flare—first increment 5 mg second 5 mg if necessary or if the patient s experience with flares dictates increment of 10 mg or so then rapid reduction as flare begins to recede If corticotropin is used doses should be about 40 per cent of those of cortisone acetate or about 35 per cent of those of hydrocortisone (free alcohol)

superimposed on irreversible changes we often use Pattern 10 In cases of rheumatoid arthritis complicated by an important relative contraindication to use of hormones such as diabetes or inactive tuberculosis Pattern 9 or 11 is appropriate For prolonged administration most workers have given cortisone orally therefore the patterns of Plan 2 are explained in terms of cortisone (Figure 24)

The important changes or refinements which have been made in the more commonly used high low dosage program have included (1) the early use and later discontinuance of priming doses (2) the introduction of dose reductions (*a*) at first unsuccessfully when the decrements were too large (50 mg) and later (*b*) successfully when decrements were smaller (formerly 12 5 to 25 mg now usually 2 5 to 10 mg), (3) the continued process of shortening the high suppressive-dose period from the early prolonged use to a period of several weeks then a few weeks and now about two weeks or less except in severe cases (4) the common use of moderate-sized suppres

oped Many workers regarded indefinitely prolonged treatment as indicated in selected carefully managed cases and the risk thereof acceptable in the face of progressive rheumatoid arthritis Prolonged uninterrupted treatment with cortisone or corticotropin has been continued for periods of 12[14,23] to 34 months[214,23–29] and more than three years for at least several patients Cortisone was selected for most cases but corticotropin has been used for a year[97] to 20 months[114] Hydrocortisone by mouth has been given continuously to 1 of our patients for more than two years

Treatment was interrupted from time to time more or less routinely by some physicians to see whether a remission had developed or to permit normalization of pituitary or adrenocortical histophysiology Predetermined rest periods at intervals of four to six months[66,133] six to eight months[187] or every 12 months[23] were recommended The rest period lasted from a few weeks[66,187] to three months[2,3]

General Results of Prolonged Administration The general results have varied considerably depending upon the selection of cases Some reports concerned only carefully selected cases of reversible disease others concerned chiefly badly disabled cripples being rehabilitated by physical and orthopedic therapy supplemented by hormones Statistics based on such mixed data are of little value

From published reports we sought answers to the following questions What happens to 100 average rheumatoid patients with reversible disease of average severity started on long term hormonal treatment? How many discontinued treatment and why? How many can continue treatment? For how long? And with what results?

In many excellent articles the results obtained in patients still under treatment are discussed but little or no information is offered about those who discontinued treatment Seven representative reports containing data on both types of patient are summarized in Tables 11 and 12 Length of treatment (usually with cortisone occasionally with corticotropin) varied from 1 to 24 months the average could not be calculated but was probably about a year Of the 216 patients who started prolonged therapy an average of 77 per cent were still being treated at the time of the reports Treatment was discontinued for four reasons (1) a clinical result insufficient to justify continuation (2) undesired effects or complications (3) a satisfactory remission with symptoms remaining in abeyance during and after graduated dose reductions to zero and (4) reasons unrelated to treatment Of the related reasons none was absolute and the reasons given in each report tended to reveal the writer s policies of treatment and dosage

The less tolerant the physician is of hypercortisonism in his patients the fewer will be the discontinuances necessitated by undesirable reactions and the more will be those ascribed to insufficient clinical results and vice versa Our own policy is revealed by the fact that only 2 of our 17 discontinuances were necessitated by undesired effects We assiduously avoid significant hypercortisonism instead using doses smaller than those preferred by many rheumatologists we reduce them if mild hypercortisonism begins to

corticotropin from 40 to 100 units daily [187, 14, 218] The suppressive dose has almost always been a fixed dose This fixed dose was given until control of the disease was obtained The period varied from 9 days in mild cases to 18 in severe cases [83, 109]

Such doses were often unnecessarily high sometimes much too high Among our first 100 patients given cortisone orally [75] satisfactory suppression was obtained (usually within two weeks or less) in 31 per cent by daily doses of 75 mg or less and in 20 per cent by 50 mg daily

The time spent in progressing from suppressive to maintenance doses varied from about 10 days to 10 weeks, this time depends chiefly upon severity the size of the decrements and the number of test days for each new dose [14, 19] Decrements of cortisone varied from 5 to 25 mg The test period for each lower dose was 3 to 14 days Thus patients were usually seen once or twice a week, sometimes every 10 to 14 days then the next lower dose was used if progress was satisfactory

Maintenance dose originally meant the smallest dose sufficient to control the patient's symptoms satisfactorily but not necessarily completely without significant undesirable effects it refers to maintenance of an optimal result not to maintenance of a dose Thus as a rule the maintenance dose should provide an optimal not a maximal response [78, 81, 90, 15, 153] But the maintenance dose cannot accomplish the same results for the badly crippled as for patients with reversible disease It should enable the latter to perform daily routines [61, 112]

Misinterpretation of the meaning of the term maintenance dose has led in many cases (1) to the protracted use of a maintenance dose that was either too high for the patient or needlessly high for the disease so that hypercortisonism developed slowly and insidiously and (2) to the premature acceptance of the idea that in all cases treatment would be required indefinitely with the consequent abandonment of effort by physician and patient eventually to taper the dose to zero

The optimal maintenance dose must be individualized as requirements vary not only in different patients but in the same patient from time to time A year or two ago maintenance doses of cortisone were usually 50 to 75 mg occasionally larger or smaller [75, 13] When moderately low, "safe" maintenance doses were reached, there was some tendency to relax effort to lower the dose further But further reduction especially if done very gradually was often performed successfully Thus maintenance of relief was ascribed to daily doses as low as 6 25 to 12 5 mg of cortisone [153, 214] and 2 to 12 units of corticotropin [85, 86, 150, 153, 214, 220–2]

With regard to duration of prolonged treatment the two customs prevailing were indefinitely prolonged treatment and routine interruption of treatment at predetermined intervals Prolonging treatment indefinitely was customary among physicians who had rarely seen a spontaneous remission during course treatment It was also customary in treating a patient who responded well to treatment but relapsed after each of one or more courses Treatment was not interrupted unless intolerance or refractoriness devel

216 patients who began treatment results were very satisfactory in 56 per cent because 5 per cent had gone into a remission (completeness not stated) and 51 per cent had received marked or very marked relief from continuing treatment

Table 12

RESULTS OF PROLONGED HORMONAL TREATMENT OF RHEUMATOID ARTHRITIS PATIENTS STILL RECEIVING TREATMENT

Reference	*Patients Still Continuing Treatment*		*Symptomatic Relief from Continuing Hormonal Treatment Percentages**				
	No	*Per Cent*	*Very Marked*	*Marked*	*Moderate*	*Slight*	*Little or None*
Davison [12]	13	68	10	21	32	5	
Kuell and Schaffarzich [3]	12	71		47	18		6
Wingfield and co workers[230]	8	80	20	40		20	
Rowe and co workers	9	82	18	37		18	9
Copeman and co workers[5]	18	90	20	30	25	15	
Boland[2]	60	79	24	39	15	1	
Ward and co workers[2]	46	73	14	20	30	3	
Totals	166	77	17	34	20	5	1
Generalization		70–80	15–20	25–40	15–30	5–10	

* Percentages are all calculated to include the discontinuances i e on the basis of the number of patients starting treatment (216 cf Table 11 Column 4)

Excluding the discontinuances and recalculating the data in Table 12 with the number of patients still under treatment as 100 per cent (instead of 77 per cent as in Tables 11 and 12) results were as follows very marked relief in 22 per cent marked relief in 43 per cent moderate in 27 per cent slight in 7 per cent little or no relief in 1 per cent This tabulated series of 166 patients still receiving continuous treatment can be almost doubled by adding the 152 patients of Cohen [214] Holbrook [114] and Steinbrocker and associates [100] all of whom were under prolonged treatment Because figures on certain results were sometimes combined as in the case of 'marked' or 'moderate' relief and no data were given on discontinuances the statistical

progress Such reduced doses were clinically inadequate in 8 or 13 per cent, of our 63 cases and treatment was stopped

In Table 11 the discontinuances ascribed to undesirable effects or complications ranged between 3 and 16 per cent, but those attributed to unsatisfactory clinical results were a rather uniform 10 to 16 per cent This last percentage depends as much if not more upon the physician s policy regarding selection of cases as upon hormonal ineffectiveness The incidence can readily be increased by overliberality in the selection of more or less irreversible cases with minimal clinical activity

Table 11

RESULTS OF PROLONGED HORMONAL TREATMENT OF RHEUMATOID ARTHRITI
DI CONTINUANCES

C lumn 1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*		*11*	*1*
				H mo l T eatm t Disc t ued for V riou Re s								
R fer c	*D t f T e tme t (mo th)*		*P t e t St t g T at m t*	*P t ts*		*R L lat d t T t ment*	*Cli ical Re ult I suffi ci nt*	*L d n bl Eff t C m plic tio*	*F rth T at m t L ne s ry (p sth mo- al em s n)*		*T atment Bei g C t ed*	
	R g	*A*		*No*	*Per C t*	*Per C t*	*Per C t*	*P Cent*	*P t t*	*Per C t*	*N*	*Per Cent*
D ison	1 3		19	6	3		16	16			13	68
K s ll nd S h f f r t	1-3+		17	5	29			1		1	1	71
W ngfi ld a d o-w k rs	-4		10	2	20		10	10			8	80
R w d co wo k rs	5-7		11	2	18	9		9			9	8
Cop m n and c wo kers	1-10	6	20	2	10	5			1		18	90
B land	6-1	10	76	16	1		11	9	1	1	60	9
W d and o wo kers *	8- 4	15	63	1	27		13	3	7	11	46	3
T tal d rag			16	50	3	1	10	7	11	5	166	7
G ne l t on n p t g				0-30			10-15	10		5-10	0-80	

The present compilation does not support the pessimism of a few earlier workers who kept drop off tallies The inference was that of patients started on prolonged treatment few would still be receiving treatment after one or two years However it will be noted (Table 11) that the percentages in most of the categories are as good in the two larger series in which treatment averaged 10 and 15 months as in the others with shorter treatment Of the

In Boland's experience with 40 patients [3] there was a useful dissociation between the antirheumatic effects and certain metabolic effects of hydrocortisone, in that cortisone induced undesired effects tended to diminish or disappear when cortisone acetate was replaced by hydrocortisone (free alcohol) given in smaller but equally antirheumatic dose No significant dissociation was apparent among our 19 cases in which the effectiveness of hydrocortisone (free alcohol) and cortisone acetate was compared

Corticotropin Prolonged treatment with corticotropin (aqueous) has been administered to relatively few patients [33-38] Of 35 patients given corticotropin by Holbrook and associates [35] for 6 8 to 19 (average 9 6) months 20 per cent obtained complete symptomatic remission and 40 per cent more than 50 per cent relief 20 per cent had unsatisfactory results

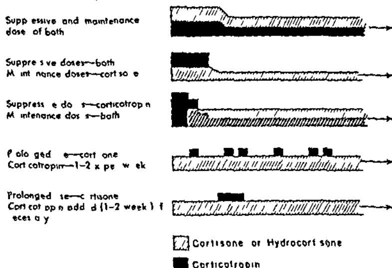


Fig 27 Combined hormonal therapy for prolonged use

largely because of progressive refractoriness to corticotropin Doses were from 10 to 40 units daily In Markson's[228] 57 patients treated from 2 to 21 months 42 per cent had excellent improvement (75 per cent or more relief), 52 per cent obtained good (50 to 75 per cent relief) and 6 per cent poor results

Progressive resistance to corticotropin has been a major problem but this has been overcome to a great extent by the recent introduction of more purified preparations

Corticotropin is not given intravenously for long periods

Corticotropin Gel No detailed results of the prolonged use of the newer preparations of long acting corticotropin in rheumatoid arthritis have come to our attention Maintenance doses of only 10 to 20 U S P units given once every day or two have been suggested [172]

Cortisone and Corticotropin Used Concurrently Concurrent use of corticotropin and cortisone is under investigation by various workers [53 90 92 239 240] but insufficient data are available for evaluation of results

analysis provided certain definite figures and certain approximations Thus of the 318 patients who continued treatment, 17 per cent (55 patients) had very marked relief and about 43 per cent, marked relief a combined figure of 60 per cent compared with 65 per cent in the smaller series (recalculated in Table 12) It would appear therefore that the smaller group is representative

Results of prolonged treatment reported by others[23] are comparable to those tabulated

Comparative Results from Prolonged Use of Different Hormones In general, clinical results in cases of rheumatoid arthritis from the prolonged use of cortisone hydrocortisone, and corticotropin have been comparable [9,78,80,33] Cortisone tablets have become the preparation of choice because of their availability and ease of administration But intramuscular injections may temporarily be preferable to the tablets under special circumstances such as acute gastroenteritis preoperative and postoperative care of hormone treated patients with rheumatoid arthritis or the rare cases of faulty absorption from the intestines [78,109]

Table 13

CLINICAL ANTIRHEUMATIC COMPARISONS*

	Approximate (average) Equivalents	
	Our Cases[7]	*Boland*[34]
Oral to oral (divided daily doses) Hydrocortisone (free alcohol) To cortisone acetate	1 1 22	1 1 59
To hydrocortisone acetate	1 1 58	1 1 97
Cortisone acetate To hydrocortisone acetate	1 1 36	1 1 35
Cortisone (free alcohol) to cortisone acetate		1 1 05
Oral (divided doses) to intramuscular Cortisone acetate oral to cortisone acetate intramuscular		*Freyberg*[81] 1 0 70 to 1 1

* Responses among individual patients vary considerably Therefore these comparisons are approximate

Hydrocortisone Boland estimated that the antirheumatic potency of hydrocortisone (free alcohol) is on the average more than 50 per cent greater than that of cortisone acetate and about twice that of hydrocortisone acetate (Table 13) Our own recent study of 31 patients confirmed Boland's general conclusions The ratios of maintenance doses as used by Boland [34] and us[78] are compared in Table 13

Doses were 37 5 to 50 mg for larger joints 10 to 15 mg for smaller joints Doses of 87 5 mg were no more effective than those of 50 mg [48] The small doses commonly used were thought to produce no systemic hormonal effect, however we have noted mild systemic effects in some cases, especially if the total amount injected at one time exceeded 37 5 mg Articular reactions occurred in about 2 per cent of the patients and were severe in degree on occasion but lasted only one to two days Complications such as infection were very rare [45]

Intra articular injections of hydrocortisone constitute palliative non specific local treatment for a systemic disease and are of limited value but under certain circumstances they may be useful as in monarticular rheuma toid arthritis or when one joint of a polyarthritis is the major problem

Other Preparations of Cortisone or Hydrocortisone Cortisone esters less soluble in plasma than cortisone acetate were no more effective than cortisone acetate Hydrocortisone (free alcohol) and hydrocortisone acetate were equally effective Therefore the superiority of hydrocortisone acetate over cortisone acetate is not related to relative solubility [24, 246, 53]

Corticotropin Injection of 20 mg into three joints produced no relief but was well tolerated [194]

Worsening of Patients during Treatment

For any patient continued relief during treatment results from the balancing in his favor of many factors When a patient s condition slowly or rapidly worsens while he continues to receive doses which previously had been effective the reason may or may not be difficult to identify The responsible change may be in (1) the activity of the disease itself (2) the patient s natural (nontherapeutic) resistance to it or (3) the utilization of the exogenous hormone by the patient s body The disease s activity is in fluenced in known and unknown ways by the aggressiveness of the unknown etiologic agent and by aggravating factors such as trauma weather changes and menses The patient s resistance can be altered by intercurrent infec tion nutritional deficits and other conditions The effectiveness of hormonal treatment can be altered by anything which disturbs the logistics involved in delivering to the peripheral cells a workable fraction of the much larger exogenous do e which the patient has taken hopefully by mouth by needle or by vein

Even though his disease and resistance remain constant the patient s condition may worsen if a significant change develops in any of the factors related to the hormone e g in its potency or purity the total daily dose (or even the division thereof) the manner of administration the fate of the hormone before or after entering the blood stream its chemical structure en route to the target cells or the responsiveness of the adrenal cortex if corticotropin is given Even though none of these factors is altered the patient s condition may worsen if the ultimate amount received by the inflamed tissues is diminished by udden hijacking activities (from an in creased need) on the part of competing nonrheumatic cells or if the capacity

of long term treatment (Figure 27) Salassa and others[164] have stated that it is improbable that corticotropin combined with cortisone or hydrocortisone will eliminate the risk of impaired adrenal insufficiency Although adrenal hyperplasia may last for some interval after use of exogenous corticotropin is discontinued "there is reason to doubt that increased functional activity of the adrenal cortex does so" Since corticotropin appears to be as effective as cortisone in producing histologic pituitary changes it would seem safest to assume that the endogenous secretion of corticotropin is depressed by exogenous corticotropin and that postoperative adrenal insufficiency is just as likely to follow corticotropin therapy as cortisone therapy '[164]

Supplemental Use of Prolonged Hormonal Therapy in the Rehabilitation of the Crippled Crippled patients are far from ideal subjects for hormonal therapy but when inflammation is still active their desire for its suppression is certainly understandable Prolonged use of cortisone during rehabilitation has given variable results, sometimes surprisingly good[80 95 113 21 41–243] sometimes negligible

One of the chief problems in treating crippled patients is the difficulty of determining the ratio of reversible to irreversible changes If a well tolerated dose gives *limited results the tendency is to increase it a little* more and then a little more in the hope of reversing the irreversible thus doses beyond tolerance are often used [44] To avoid this in such cases we have favored the use of Treatment Pattern 10

Intra articular Administration of Cortisone Hydrocortisone and Corticotropin

Cortisone Acetate Doses of 25 to 50 mg sometimes 60 to 100 mg, have been injected into the joints of 50 or more rheumatoid patients with little or no benefit[79 194 45–248] Some injections were well tolerated [47] many *caused transient local irritation* [46]

Hydrocortisone Acetate In about 250 patients local results have been more striking from intra articular injections of hydrocortisone acetate[79 34 245 48 248–53] than from cortisone given by the same route Reduction of pain swelling and stiffness and improved function developed in *85 per cent but were marked or very marked in only* about 50 per cent of the cases Relief almost always began within 24 hours often within 2 to 4 hours, it commonly lasted 2 to 7 days sometimes 2 weeks and occasionally 1 to 4 months[251 253] Articular abuse after injection tended to nullify relief Improvement might accompany the first but not later injections or *it might not* develop until after the second or third if none appeared after the third injection further injections were considered useless Results did not relate to the local articular severity Effects were rarely additive Synovial cell count and intra articular temperature were reduced Viscosity of synovial fluid was increased [253] Synovial biopsies revealed no histologic *effect from* a single injection but gave evidence of healing after several injections [248]

(4) a true rheumatoid flare, often spontaneous and related to overactivity or emotional stress

Incidence of Exacerbations The incidence of articular exacerbations during hormonal therapy has not often been reported Of 63 exacerbations experienced by 50 patients, 6 were produced by emotional upset 13 by infection 22 by dose reduction, 8 by cessation of treatment and 14 by unknown causes [59]

Resistance to corticotropin developed in 8 per cent of the 100 cases studied by Renold and co workers[201] and in 3 of 20 cases studied by Goslings and associates [85] but was not seen among patients treated by others [65 95 99 180] especially those treated with corticotropin for short terms Of 73 patients 3 became refractory in time to increasing doses of either corticotropin or cortisone [100] Resistance develops rarely, if at all from the use of the newer purified preparations of corticotropin [97 108 171 35 61] Worsening of symptoms from resistance to corticotropin given intramuscularly can best be diagnosed and treated by (1) changing the species of corticotropin (2) giving test doses intravenously or (3) switching to cortisone

The diagnosis of corticogenic hypothyroidism and the escapes blamed thereon are reportedly based upon studies of uptake of radioactive iodine and serum levels of protein bound iodine metabolic rates may be normal or low [90] In such instances 60 to 180 mg (1 to 3 grs) of desiccated thyroid extract is said to restore responsiveness [96] But detailed case reports are difficult to find and in our group we have seen no cases in which refractoriness could be completely explained by the appropriate tests or was relieved by thyroid extract [8 61] Slocumb [6] has stated that many cases of supposed resistance to cortisone represent in fact insidious commonly unrecognized hypercortisonism

Worsening Owing to "Pseudorheumatism" of Hypercortisonism * It is Slocumb's opinion [6] in which we concur that certain previously unrecognized manifestations of hypercortisonism superficially simulate arthritic symptoms in rheumatoid patients and in patients who have lupus erythematosus In the past these symptoms often have been erroneously considered flares of rheumatoid arthritis occurring either spontaneously or because of resistance to hormones Manifestations of the pseudorheumatism of hypercortisonism must be differentiated from true rheumatoid flares since the presence of hypercortisonism is an indication for reduction rather than increase in dose of hormones (Table 14)

Manifestations The symptoms consist mainly of (1) excessive fatigability with weakness (2) aching in muscles and joints often diffuse and (3) emotional instability In contrast to the fibrositic symptoms of a true rheumatoid flare these are made worse by physical or mental effort and are improved by rest Aspirin heat and physical therapy do not help much, if at all although at times the rest associated with some treatments does give temporary relief Symptoms tend to be cyclic Periods of restless energy mental

* The term hypercortisonism is used here in a non specific inclusive sense indicating effects of excessive doses of cortisone hydrocortisone or corticotropin

of the inflamed cell to respond to its previously adequate hormonal allowance is suddenly altered. The continuing effectiveness of a given dose taken by mouth depends, at the least, upon the relative constancy of its absorption by the intestines or the degree of its (presumed partial) inactivation by the liver, through which most of it must pass. To be constantly effective intramuscular doses must continue to undergo the same sort of reception and handling by the tissues as that which they had previously met. Even doses of equal size given intravenously must, having run the gauntlet of the several organs which are capable of altering them, be comparable in size and strength when they reach the peripheral cells.

When all these factors are considered it is a wonder that rheumatoid patients are "stabilized" as often as they are by the continued use of essentially the same dose from day to day.

In the precortisone era (the gay bachelorhood of rheumatology before the latter's sudden thought provoking union with endocrinology) the worsening of a rheumatoid patient was explained simply as a rheumatic flare and that was that. But now one must try to differentiate between a true simple uncomplicated rheumatoid flare, a worsening due to underdosage, a pre- or post-withdrawal articular rebound, and worsening ascribed to hormonal unresponsiveness, inactivation, refractoriness, resistance, addiction or "escape."

Articular exacerbations have been blamed on the following actual or hypothetic developments: (1) reduction in dose, use of a smaller test dose which proves to be inadequate, (2) inappropriate division of the day's total dose, (3) a change in route of administration, as from a dose of cortisone given orally to the same dose given intramuscularly, (4) temporary refractoriness, resistance or unresponsiveness to corticotropin or cortisone, (5) corticogenic hypothyroidism induced by cortisone or corticotropin, (6) severe cachexia, (7) emotional upsets, (8) intercurrent infection, (9) trauma from overexertion, (10) changes in weather, (11) spontaneous flares or increased severity of the rheumatic process, (12) adrenal unresponsiveness to corticotropin, (13) adrenocortical dysfunction from disturbed cortical metabolism, (14) ascorbic acid deficiency, (15) altered adrenocortical responsiveness, reduction of output of endogenous cortisone, (16) formation of antibodies to corticotropin itself regardless of species of the source, (17) increased tissue requirement or need resulting from superimposition of various stresses, (18) increased tissue desire or habit, the adaptation of tissue cells to the higher levels of circulating steroids ("cortisone addiction"), (19) development of skeletal symptoms (from hypercortisonism) simulating but not constituting a true flare, and (20) progressive withdrawal of hormones.[85, 88, 90, 96, 101, 109, 139, 171, 01, 07, 54–258]

Of the many mechanisms which may actually or hypothetically produce a rheumatism-like flare during hormonal treatment these four seem to us to be most definite: (1) a transient flare from any single improperly judged dose reduction, (2) development of resistance to corticotropin injected intramuscularly, (3) diffuse "pseudorheumatism" of hypercortisonism, and

Table 14—(Continued)

	Rheumatoid Exacerbation	*Pseudorheumatism of Hypercortisonism*
Effect of (continued) Physical therapy	Usually helpful	Poorly tolerated especially if fatiguing
Aspirin	Usually helpful	Doses of 2 6–3 2 Gm daily usually of only slight benefit
Effect of cortisone Total daily dose	Insufficient for current activity of disease	Excessive production of hypercortisonism
Single fraction of day s dose e g the next regular dose	Little or no relief even temporarily	Transient partial relief re priming effect lost in 4 to 10 hours
Increased total daily dose	Relief if increase sufficient	Emotional instability increased musculoskeletal symptoms and fatigue may be better temporarily but eventually will be worse
Gradual reduction of dose	Patient becomes worse	Patient improves with or without temporary aggravation for a time after each reduction
Psychic features	Discouragement proportional to severity of disease	Mood fluctuates euphoria and restless energy alternating with emotionalism irritability and mental as well as physical fatigue
Cerebration	More or less normal	Memory for details poor
E S R	Increase usually proportionate to flare	May remain hormonally depressed even normal but may slowly increase as hypercortisonism increases
Other manifestations of hypercortisonism	Often none present	Usually present although often slight

stimulation euphoria and relative freedom from musculoskeletal symptoms which may follow rest or a dose of cortisone will alternate with periods of weakness exhaustion diffuse aches and pains and emotional instability to the point of crying The latter periods are apt to occur when the patient is fatigued or when the effect of the last dose of cortisone has waned Symptoms of hypercortisonism have appeared within a month of starting treatment with large doses but may not appear for many months if smaller but still excessive doses are employed Although women especially if post menopausal are more prone to develop these evidences of hypercortisonism the symptoms also occur in men

Table 14

PSEUDORHEUMATISM OF HYPERCORTISONISM DIFFERENTIATION FROM A RHEUMATOID EXACERBATION

	Rheumatoid Exacerbation	*Pseudorheumatism of Hypercortisonism*
Patient s common complaint	My *joints* are worse	*I m* worse—worse all over
Chief characteristic	Usual arthritic exacerbation characteristic synovial fibrositic and systemic worsening	Cyclic swings (of a few hours) from comfort and energy to aching fatigue depression Complaints more diffuse vague pain soreness aching stiffness Patient may vary terms and complaints
Relation of subjective complaints to objective data	Proportional	Disproportionate subjective complaints out of all proportion to objective findings
Chief location	Joints fibrous tissue	Muscles and joints usually diffuse ache all over
Energy and motivation	Likely to be decreased	Cyclic changes spurts of energy and restless drive later fatigue
Articular symptoms	Increased	Often no increase when patient is rested
Signs	Increased synovitis	Little or no increase in synovitis still hormonally suppressed
Muscular symptoms	May be increased but usually less than in joints	Prominently increased
Signs	Tenderness of muscles usually less than that of joints	Marked generalized tenderness often more marked in muscles than in joints
General response to examination	Characteristic of severity of disease	Hypersensitive often touch me not reaction as in psychogenic rheumatism
Effect of		
Rest	Increased jelling	Patient feels better unless effect of previous dose of hormone has worn off
Exercise	Patient may feel better	Patient feels worse particularly if activity is fatiguing
Heat	Usually helpful	Little benefit except from associated rest

2 and negative for both in 1 The effects of roentgen therapy were less dramatic but lasted longer [263]

Certain spondylitic patients are given combined physical therapy and roentgen therapy, later hormones if necessary In some cases roentgen therapy inadequate by itself might be given during prolonged use of cortisone Opinions on the protective action of cortisone against irradiation sickness have differed The deleterious effect of total body irradiation of mice was enhanced when cortisone was given just before irradiation [269] But the roentgen doses used for spondylitis are so low that the combination seems without danger to man [270]

Juvenile Rheumatoid Arthritis Still's Disease Juvenile rheumatoid arthritis or Still's disease [89 99 0 227 271–76] commonly remains active for years and does not often stop at puberty Interference with epiphyseal growth may lead to excessive deformities Amyloidosis [77 278] develops frequently [27] Mortality rates in recent studies were 8 to 34 per cent at an average age of 13 5 years [2 7 277 78] The doses of hormones required for treatment have depended more upon the severity of the disease than upon the child's size or age Certain policies of others have been to give (1) as the optimal initial dose the smallest amount producing painless articular movement [71] (2) for small children about half the adult dose for larger children nearly the adult dose [03] (3) as the maintenance dose about 1 mg for each kg of body weight [103]

Daily initial or suppressive doses of cortisone varied depending upon the severity and age of the child from 25 to 100 mg [99 103 2 7 71 275] of corticotropin from 15 to 60 units [97 79] Maintenance doses of cortisone were usually 25 to 50 mg of corticotropin 1 to 10 units [97 0] Small maintenance doses of a European brand of corticotropin 1 to 4 units daily were reported successful [89 0] Treatment was commonly given in courses of 10 to 30 days each but was continued satisfactorily by some investigators for several months [99 103 191 271] to 665 days [227] Remissions seemingly developed more often in children than in adults

In general children developed the same undesired effects as did adults but these usually occurred earlier in the treatment since the doses required were greater per pound of body weight A few children given corticotropin tended to have hypertension (this happened less often with cortisone) or convulsive phenomena more frequently than did adults [79 80] and 1 child died after a sudden convulsion [71] Fluid retention and possibly cerebral edema may have been responsible Because of this several physicians recommended salt restriction for children receiving these hormones [97 79 81] No edema developed when salt was restricted Children often were ravenous and the fat girl syndrome was noted [271] Hence the caloric intake should be not in excess of that required for normal weight and growth

Studies were made to see whether the hormones would interfere with the growth of children who already tend to have growth disturbances As retardation of general growth from hormonal therapy has been noted in nonrheumatic children it probably can occur in children with rheumatoid

The musculoskeletal symptoms resemble somewhat those of psychogenic rheumatism Aches and pains tend to be diffuse rarely localized to joints or specific areas of muscles The patient is frequently hypersensitive, and the touch me not reaction is often exhibited upon initial pressure on a certain spot whereas repeated pressure on that site may elicit noticeably less marked tenderness Symptoms tend to be out of all proportion to the objective evidence of synovitis which may be almost as well suppressed as it was in the earlier days of the treatment when results were satisfactory The E S R varies It may be low or not increased in proportion to the complaints or, if the hypercortisonism has progressed it may be high

Increase in dose of hormone may afford temporary relief of musculoskeletal symptoms and fatigue but psychomotor symptoms and other objective manifestations of hypercortisonism are increased, after a time even the musculoskeletal symptoms recur and gradually become worse than ever On the other hand with each small reduction of dose the symptoms may be aggravated, but improvement will follow after several days—rarely longer

Treatment These reactions are treated by gradual small reductions in dose of hormone to permit disappearance of all manifestations of hyper cortisonism, this may require one to three months or more often under supervision in the hospital if the reaction is severe Details are accomplished as discussed under Systemic Withdrawal Reactions—Prevention and Treatment—pages 239–242

The Variants of Rheumatoid Arthritis

Results of treatment of these conditions with cortisone and cortico tropin as well as untoward effects and schemes of doses except for children were the same as in peripheral rheumatoid arthritis

Rheumatoid Spondylitis In early or not too far advanced cases of this disease results of hormonal treatment were good to ' spectacular [63 10 1 3 63] but disappointing in the severe cases [63 107] Ligamentous calcification and ankylosis of spinal joints were not affected Short term use was valuable for acute exacerbations [263] also for arthroplasties done under the protection of cortisone [64 265]

Ocular lesions develop in about 20 per cent of patients with rheumatoid spondylitis [266] Rheumatoid iritis was benefited by these hormones [1 3 1 7 267] but removal of bilateral cataracts under the protection of cortisone was followed by formation of cyclic membranes [267] and occasionally when treat ment of iritis was discontinued the other eye became affected for the first time [127]

Our spondylitic patients with peripheral rheumatoid arthritis have responded to continued use of hydrocortisone [78]

Roentgen and Hormonal Therapy Roentgen therapy is still generally regarded by some as the treatment of choice in most cases of rheumatoid or ankylosing spondylitis [9 66 100 102 21 68] In a comparative study of the effects of roentgen therapy and of short term cortisone therapy in 5 cases Hart [63] noted that results were better from roentgen therapy in 2 patients equal in

undesirable effects as well as a few useful guides to the control of treatment but nothing definite on the basic mechanism of relief has yet been revealed Although antirheumatic effects are usually accompanied by characteristic biochemical reactions dissociation of the relief from any of the physicochemical reactions studied to date is common Furthermore the latter are widely modified by the responsiveness of each patient

Following are characteristic responses to hormonal therapy depending upon dosage and length of treatment All references refer to patients with rheumatoid arthritis unless stated otherwise Much of the data reported are derived from investigative procedures and are not from routine laboratory studies

Data Related to Blood and Circulatory System ***Sedimentation Rate*** About 90 per cent of patients with active rheumatoid arthritis have elevated E S R s[107, 271, 99] During hormonal administration the E S R generally is reduced usually markedly and rather promptly but sometimes slowly or incompletely Clinical results have sometimes been excellent although E S R s have remained high[99, 112, 114, 180, 59, 300] Conversely the E S R may decrease notably yet the clinical response may be poor or disproportionate[113, 114, 180] Reduction of the E S R bears a general but not an absolute relationship to dosage At the onset of treatment there is often a delay of 3 to 12 days[9, 206] before the E S R starts to decrease even though relief may have been prompt In repeated courses responses to comparable doses are about the same

Relapses during treatment are not always associated with increasing E S R s nor does a sudden increase during treatment necessarily indicate an impending relapse But significant or progressive clinical worsening is commonly associated with an increase in the E S R

Sedimentation Rates as Guides to Treatment Estimations of the E S R have a strictly limited value in this respect The trend of the rate is useful not the rate at a given time One should not at the onset of treatment wait to reduce the initial dose until the E S R has started to fall for the rate generally falls as dose reductions are made unless decrements are too large Above all one must not treat the E S R The patient s status (subjective and objective) and not the E S R should be the basis for changes in doses But whenever the rate begins to increase steadily investigation is in order The increase may indicate (1) significant underdosage which is or will be accompanied by lessened relief (2) the presence of some complication minor or major (3) any of the situations related to flares and also apparently to progressive hypercortisonism even though the E S R is not commonly increased in Cushing s syndrome[9, 31] and (4) on occasion the development of mild rheumatic or rheumatoid carditis[71]

Sedimentation Rates after Treatment After cessation of treatment the E S R usually increases sooner and more markedly than do symptoms This is another example of dissociation The E S R then generally approaches its pretreatment limits but occasionally it may increase quickly to a level higher than that reached before treatment

arthritis if excessive doses are used But no such retardation was noted as a rule in rheumatoid children treated for a few weeks (courses) or for as long as 9 to 22 months [10 103 7] Wilkins and associates [5] noted evidence of retarded growth in a child with adrenal hyperplasia Diets liberal in protein help to neutralize the anti anabolic effect of cortisone [81]

Rheumatoid Arthritis with Splenic Neutropenia Felty's Syndrome Rheumatoid arthritis with splenic neutropenia has responded to cortisone[293 84] and to corticotropin [148 149] The joints and the blood picture improved during treatment Splenomegaly disappeared completely in 1 case diminished only slightly in others

Rheumatoid Arthritis Associated with Other Diseases

Hypopituitarism Simmonds' Disease, Sheehan's Syndrome A minority of patients with hypopituitarism have stiffness or joint pain [85–87] particularly of the knees but definite associated rheumatoid arthritis apparently is rare In a case reported recently,[288] articular response to corticotropin was equivocal Objective and subjective improvement resulted from cortisone but disappeared after the second course

Addison's Disease Articular and periarticular pain have developed in patients with Addison s disease who were given desoxycorticosterone acetate (DCA) [89–91] Although the association of rheumatoid arthritis with Addison s disease is rare a few cases have been reported recently [292–96] In 3 cases the arthritis improved dramatically with use of cortisone in daily doses of 25 to 100 mg [9 93] Corticotropin 45 units daily relieved joint pain but not fatigue In 1 case [93] an articular flare occurring during the use of DCA disappeared when cortisone was substituted, initially 25 mg of cortisone daily was not entirely adequate for the relief of joint pain but later it was effective

Diabetes Mellitus Beginning in 1919 and for years thereafter Pemberton and others considered that carbohydrate metabolism was disturbed in rheumatoid arthritis because the glucose tolerance curves so commonly resembled those of mild or latent diabetes But frank diabetes rarely affects patients with rheumatoid arthritis which is fortunate in view of the effect of cortisone and corticotropin upon carbohydrate metabolism [297] Most nondiabetic arthritics respond to these hormones without glycosuria or notable changes in blood sugar [141 298] However diabetic patients with rheumatoid arthritis who are treated with hormones generally have developed an increase of glycosuria and hyperglycemia As a rule this has required intensification of treatment of the diabetes whether by diet insulin or both [97] Insulin resistance may increase during treatment and decrease on withdrawal

Effect of Hormonal Treatment of Rheumatoid Arthritis upon Laboratory Data

Biochemical, metabolic and other laboratory data have given us some understanding of the development correction and prevention of certain

no significant alteration in clotting time of whole blood and pointed out possible errors in methods used by others

These hormones produce a dramatic fall in plasma fibrinogen[309] which parallels but antedates that of the E S R [310] by 24 to 48 hours During relapses after cessation of hormonal therapy concentration of plasma fibrinogen often rebounded as much as 50 per cent above pretreatment values increases which often were not reflected in the E S R

Serum Proteins In rheumatoid arthritis serum proteins may be normal or abnormal Serum globulin is often increased so that albumin globulin ratios are reversed In general cortisone reduces the concentration of globulin but does not affect serum albumin Total proteins were reduced at the expense of globulin and albumin globulin ratios were unchanged or slightly increased Variations of these results have occurred [79] Values for alpha and gamma globulins increased before treatment [311] were usually but not always decreased during treatment [309, 31] as measured by zinc sulfate turbidity [35] and electrophoretic patterns [82, 313] The normalization of protein patterns of serum and synovial fluid during hormone induced remissions resembles that seen during spontaneous remissions [134]

Miscellaneous Blood Studies C reactive protein commonly present in the serum of rheumatoid patients disappears during use of corticotropin [314] During hormonal therapy hexosamine has decreased in blood and increased in urine [82, 2 0] The cephalin flocculation test which was positive before treatment in 2 cases became more positive in 1 and negative in another during treatment [78, 134]

The thymol reaction often is positive in rheumatoid patients During hormonal therapy it may become normal [315] In 1 case [8] the serum tryptic inhibitor level was above normal before and after use of corticotropin during treatment it became normal The level of nonspecific hyaluronidase inhibitor in blood and the histaminolytic activity of blood were decreased during treatment [82, 2 0] Concentrations of plasmin plasminogen and anti plasmin in citrated plasma were normal during treatment [2 0]

The values of serum inorganic phosphorus may be temporarily decreased [28] those for serum alkaline phosphatase are not altered during treatment [35, 0] Serum iron which is sometimes low in rheumatoid arthritis may or may not increase and the iron tolerance test may be influenced [84, 316] Hypercupremia sometimes present in rheumatoid arthritis decreased during use of corticotropin and increased after withdrawal [316] Among certain rheumatoid and other patients hematocrit readings increased 2 to 6 cc per 100 cc of blood [30, 304] Plasma volume may increase [30, 303] or decrease depending upon the degree of sodium retention The value of packed red cells may rise without reticulocytosis [316]

Capillary Resistance and Permeability Capillary resistance was increased by cortisone or corticotropin given to rheumatoid patients However in patients with hypercortisonism capillary resistance may be diminished as evidenced by easy bruising and spontaneous petechiae [317, 318] Cortisone inhibits the increased capillary permeability produced in animals by in

Hemoglobin If the concentration of hemoglobin is subnormal—as is often the case in rheumatoid arthritis—it usually increases slightly (from 1 5 to 4 5 Gm per 100 cc) during treatment but may decrease after treatment is stopped [9, 84]

Blood Counts If anemia is present and favorably affected, the erythrocyte count may increase to or toward normal by 500,000 to 1 000 000 cells per cu mm The development of polycythemia has not been reported

In rheumatoid arthritis leukopenia with relative lymphocytosis is commonly present During treatment the leukocyte count increases to an average of 3,000[150] to 21 000[30 –304] cells per cu mm polymorphonuclears may increase notably Lymphocyte counts may be increased decreased or unchanged [35 95 180 0 304] Monocyte counts have been unaltered[34 95] or slightly increased

Eosinophils are far more sensitive than are other blood cells to these hormones Eosinopenic responses to various standard doses of corticotropin are widely used as tests of adrenocortical function before during and after hormonal therapy Such tests although they have given useful information have limitations [305] Eosinophil counts vary in different persons and in the same person at different times even within one day they are transiently influenced by numerous factors including emotion and different batches of corticotropin Antirheumatic doses of corticotropin usually produce marked eosinopenia at least at the onset of treatment [79 115 116] but a good clinical response is not always accompanied by notable eosinopenia, and vice versa [79 95 14 3] As use of corticotropin is continued eosinophilia may develop slowly a change of species of corticotropin may restore the eosinopenia [0]

The eosinopenic potency of cortisone varies with the dose and method of administration High and moderately high doses given intramuscularly to our patients were slowly absorbed and produced relatively constant blood levels of hormone without significant eosinopenia [35] Oral or intravenous administration of cortisone usually affects eosinophils notably but dissociated effects have also been common Therefore we and others[305] have not regarded serial eosinophil counts as reliable measurements of the efficacy of hormonal therapy

Reticulocytosis usually develops at least transiently [89 95 302 303] Only minor changes in platelet counts have been reported [95 302 303] The thrombopenia of a child with severe rheumatoid arthritis disappeared for a while during use of corticotropin [89]

Coagulation Factors Studies have been made to account for certain thromboembolic complications of hormonal therapy Coagulation (clotting) time and heparin retarded clotting time of venous blood may be considerably shortened The former was reduced from 20 to 9 minutes by use of 100 mg of cortisone daily for 6 days in 1 rheumatoid patient [306] Reports on prothrombin time and on protamine titers have conflicted [306 307] Platelets are not altered and during hormone usage responsiveness to dicumarol is normal or increased not decreased [306] Fahey [308] using a new method found

Blood urea does not increase unless renal insufficiency is present coinciden tally e g in renal amyloidosis

Concentrations of uric acid may be decreased slightly in serum[45 2 0] increased in urine[28 35] during treatment Creatinuria may be temporarily increased if large doses are used [3 3]

Abnormal metabolism of amino acids may be present in untreated rheumatoid arthritis as shown by subnormal concentrations of free arginine histidine and threonine in plasma increased urinary excretion of bound tyrosine and decreased excretion of free histidine During treatment with cortisone or corticotropin the concentrations of histidine in plasma and of histidine threonine and tyrosine in urine are increased Such urinary changes have been observed only during spontaneous remissions or in those occurring with jaundice or pregnancy and have not been produced by a variety of other antirheumatic or other remedies[99 326–330]

Data Related to Carbohydrate Metabolism Hormonal therapy has rarely produced significant impairment of carbohydrate metabolism in rheumatoid arthritis Glycosuria is usually absent but sometimes occurs transiently, unless coincidental diabetes is latent or impending[9 5 112] Renal glycosuria (not steroid diabetes) in a patient with rheumatoid arthritis may be un covered on administration of these hormones[331 33] The blood sugar may be transiently increased but is usually within normal limits it is not associated with glycosuria These increases result from suppressive rather than mainte nance doses of hormones[29 79 333]

Glucose tolerance tests are commonly normal before and during treat ment but in several rheumatoid patients results that were abnormal before use of hormones became normal during treatment and then re turned to abnormal after treatment[9 107 113] Occasionally carbohydrate tolerance has been slightly impaired during hormone administration but usually has become normal within two to three weeks after discontinuance of treatment[3 113] Blood glutathione is not significantly altered[35 113 331 334]

Data Related to Fat Metabolism Serum cholesterol and phospholipids have been increased in animals and in man by prolonged use of the hor mones[33] but the changes among rheumatoid patients have been moderate or minimal[29 35 0] Bloom and Pierce[336] found no characteristic alteration in serum lipoproteins from hormonal treatment and no relationship between such treatment and atherosclerosis

Data Related to Metabolism of Bone Osteoporosis and spontaneous fractures have complicated cases of Cushing s syndrome and a few cases of rheumatoid arthritis during hormonal therapy Cause of the fracture is not completely understood in all instances but in some cases it probably has been related to increased osteoporosis which in turn was secondary to negative nitrogen balance Calcium metabolism is usually not altered not-ably[35] Serum calcium and the calcium content of bone as shown by special roentgenograms are generally unchanged[0 3 4] Sjogren[3 5] noted inconsistent changes in calcium balance from cortisone although urinary excretion some-times increased significantly

jected leukotaxine or an alkaline exudate, it does not affect the increased permeability induced by an exudate which has become acid and which may be related to the substance exudin.[319, 3 0] *Per contra*, corticotropin inhibits the latter but not the former type of increased permeability.

Bone Marrow Cytology of bone marrow was not altered by intramuscular use of cortisone or corticotropin for one week.[3 1] After longer treatment with cortisone, in several cases a general cellular increase, especially of granulocytes, and a relative decrease of plasma cells occurred,[95, 3 2] corticotropin produced a decrease in cells, especially plasma cells, or normalization of bone marrow in 4 cases. Phagocytosis increased.[8, 94, 31] One investigator observed that hormones exerted no notable effect upon normal bone marrow.[3 3]

Electrocardiograms The ECG generally is unaffected unless hypopotassemia is induced by overdosage. In that event T waves may be low, isoelectric or inverted, and the S T segment depressed.[9, 59]

Metabolic Studies in Rheumatoid Patients Rheumatoid arthritis has its characteristic biochemical and physiologic abnormalities which modify somewhat the usual physiologic effects of the hormones per se. Thus some of the hormonal effects require special interpretation.[9, 35, 261, 3 4 3 5]

Large daily doses of cortisone (200 mg for a short time or 100 mg for a longer time) or of corticotropin (100 units or more for days or weeks or 40 to 50 units or more for a longer time) may produce negative nitrogen balance and transient hypochloremic hypopotassemic alkalosis. But the doses commonly used today generally produce no significant alterations in plasma electrolytes or in the balances of sodium, potassium, chlorides or nitrogen. During use of the larger initial doses there may be a tendency for an initial retention and later a liberation of salt and water and reduction of serum potassium. But these changes are as a rule transient and may disappear even before doses have been reduced materially.

Isolated tests of blood electrolytes are of limited value and a transient elevation of serum sodium or a reduction of potassium may have little significance unless associated with the appropriate clinical evidences of hypercortisonism, among which are the characteristic electrocardiographic changes. Concentrations of serum potassium may be momentarily subnormal without symptoms.[9, 28]

The basal metabolic rate is occasionally a little increased as a result of the rheumatoid arthritis, not hyperthyroidism. During hormonal therapy it may decrease as the arthritis improves.[9]

Among our rheumatoid patients there have been no consistent changes in the respiratory quotient[35] induced by treatment.

Data Related to Protein Metabolism Protein catabolism is affected by large doses as indicated by increased excretion of nitrogen, uric acid and creatine. But no such changes are measurable during use of the doses now generally employed. Minimal increases in excretion of nitrogen may result from suppressive doses but not from maintenance doses.[35, 0]

Albuminuria and proteinuria are seen rarely among rheumatoid patients during treatment; if they develop, amyloidosis should be suspected.[0]

Effect of Corticotropin upon 17 Ketosteroids In adults with responsive adrenals corticotropin promptly increases the excretion of 17 ketosteroids Significant increases have been noted in some rheumatoid children but not in others[89 2 0 79] Among our adult patients excretion during treatment varied between 21 and 14 mg per 24 hours as compared with 1 8 to 11 7 mg before treatment When use of corticotropin was discontinued excretions decreased rapidly to prehormonal amounts[9 35 304]

Corticosteroids in Rheumatoid Arthritis before Treatment Among our rheumatoid patients the precortisone excretion of corticosteroids has ranged from about 0 2 to 2 0 mg At this clinic the normal daily excretion of corticosteroids is considered to be 0 3 to 1 2 (average 0 56) mg in men and women Thus values in rheumatoid patients have been normal generally though sometimes subnormal on a single determination They were subnormal in 4 of the 20 patients of Copeman and associates[95]

Effect of Cortisone upon Corticosteroids Daily excretion increases but rarely to more than 5 mg per 24 hours with usual doses the initial increase may taper off later excretions being more nearly normal[9 95] After use of cortisone is discontinued the urinary concentrations of corticosteroids gradually become normal again[193]

Effect of Hydrocortisone upon Corticosteroids In general the excretion of corticosteroids has been increased by hydrocortisone much as by cortisone[16 193]

Effect of Corticotropin upon Corticosteroids Excretion of corticosteroids is usually promptly and markedly increased Among our patients the excretion varied between 3 3 and 17 5 mg per 24 hours[9] After discontinuance the increased excretion disappeared quickly[9 35 304]

Evaluation of Urinary Steroids Estimations of urinary steroids are not used as guides to treatment because methods are too laborious for routine use and their accuracy is relative Over all results have followed a characteristic trend but in individual cases results have varied greatly and a satisfactory clinical effect may develop without the usual urinary changes[113]

For research purposes estimations of urinary steroids have been informative[89 95 345–349] The ratio of etiocholanolone to androsterone is greater in rheumatoid patients than in normal persons before and during use of cortisone according to Copeman and his associates[95] Corticotropin increased the urinary excretion of etiocholanolone especially[89] Such deviations were looked upon as not necessarily peculiar to rheumatoid arthritis

Quantitative and also qualitative changes in the steroid pattern of rheumatoid patients were described by Dobriner and associates[347–3 0] Before treatment such patients excreted the normal steroid hormone metabolites at a consistently low normal level This finding suggests that a quantitative deviation from the normal excretion pattern may be characteristic of rheumatic diseases Since the steroid excretion reflects the hormone production there is presumed to be a decreased hormone formation by the adrenal glands in rheumatoid arthritis A striking qualitative abnormality' also was found Four of the five patients studied excreted a

Miscellaneous Metabolic Studies Excretion of glucuronic acid and gentisic acid in urine was not increased by use of hormones [8] A chromogen believed to be homogentisic acid was reported in the urine of 1 patient [33] Excretion of hexosamine was found to be increased by hormones [8 20]

Serologic (Immunologic) Data The sera of rheumatoid patients have an increased capability of agglutinating alpha and beta streptococci, staphylococci and red blood cells of sensitized sheep Certain changes in circulating antibodies have been reported but the serologic abnormalities most characteristic of rheumatoid arthritis have remained abnormal during treatment [28] Increased titers of streptococcic agglutination remained unchanged throughout treatment in some cases [9] and became normal in a few [8 31] The antistreptolysin titer decreased or remained low [29 30 31] the antistaphylolysin titer decreased[312] or was unchanged [28] Agglutinations to red blood cells of sensitized sheep were reported to be unaffected by corticotropin [337] Complement activity, normal or increased before treatment tended to diminish during use of corticotropin [310]

Synovial Fluid and Membrane The increased cell count of synovial fluid of rheumatoid patients is notably decreased or normalized by hormones viscosity is increased greatly and the proteins become normal [134] The permeability of synovial membrane is not altered notably [338] Knee blood flow is increased and finger tip temperatures are decreased in untreated patients these tendencies are reversed by corticotropin [117]

Electroencephalograms These have shown evidences of increased cerebral activity during treatment increased frequency of alpha waves [4] and ' slow activity at the vertex [28 134]

Urinary Excretion of Steroids *17 Ketosteroids in Rheumatoid Arthritis before Treatment* Reported concentrations have varied from normal in 70 to 80 per cent of the cases to low in 20 to 30 per cent [9 339 340] In rheumatoid spondylitis average concentrations have been reported as above normal[341] or relatively low [95 135 339 34 343] Among our patients values have been generally normal for males with peripheral arthritis and sometimes as low as 2 4 mg for females with peripheral arthritis or 3 7 mg for males with spondylitis [9]

At this clinic the normal daily excretion of 17 ketosteroids is considered to be 6 to 20 (average 14) mg for men and 4 to 17 (average 10) mg for women [344]

Effect of Cortisone upon 17 Ketosteroids The effects of cortisone have varied depending upon the pretreatment excretion and upon dosage and duration of treatment In general with daily doses of less than 100 mg of cortisone urinary excretion decreases notably at the onset of treatment and may fluctuate during treatment but usually remains lower than the precortisone level as long as treatment is continued and until the cortisone induced inhibition of adrenocortical function has disappeared after treatment [9 95]

Effect of Hydrocortisone upon 17-Ketosteroids Our results with hydrocortisone (free alcohol or acetate)[78] showed trends comparable to those from cortisone, i e variable reductions in the excretion of 17 ketosteroids [16 193]

difference between a physiologic dose of these hormones and a pharmacologic or pathologic hormonal dose

The matter of definitions and distinctions is difficult becau e we do not know the precise quantitative differences between the physiologic and the pharmacologic dose on the one hand and between the pharmacologic and pathologic on the other

From physiologic and clinical studies one would conclude that it is not the 'manufacturer' (the adrenal cortex and its day s output) but the customer (the peripheral cells and their ever changing or potentially changing need and utilization of the hormone) which decides the physiologic dose for any given day Whether a hormonal dosage (endogenous or exogenous) is physiologic pharmacologic or pathologic is a two-dimensional affair—one of do e plus time A high briefly u ed increment or a lower but longer used increment could be either physiologic or pathologic depending upon circumstances A person s physiologic need for a hormonal increment could be 1,000 mg used up in 5 days as for a major surgical operation or 1 000 mg spread over 50 days The same increment 1 000 mg within 50 days or 20 mg daily would be physiologic if needed and utilized pathologic if not needed or not utilized to the patient s advantage With these points in mind perhaps we can approach the problem of differentiating between side effects and complications of hormonal therapy

Discussion of side effects in patients who have rheumatoid arthritis hould be confined to those effects which exaggerated doses can produce in a person who is normal except for rheumatoid arthritis Thus two primary factors are involved in the production of this kind of side effect the do age and the disease or the dosage and the tissues as they are characteristically altered by rheumatoid arthritis Whatever exaggerated doses can produce in a rheumatoid patient who is otherwise normal is a side effect of the hormonal therapy of rheumatoid arthritis an effect less general than some suppose

In the hormonal treatment of rheumatoid arthritis per se true diabetes never develops and even steroid diabetes is uncommon If true diabetes were to develop in a rheumatoid patient it should be classified as a complication not as a side effect This means that a third factor must have entered the picture namely latent or quiescent diabetes

In rheumatoid arthritis then ide effects may be considered to be those effects which according to judgment based on experience with various do ages in many patients having only rheumatoid arthritis could result from overdosage without the intervention of any possible third factor A complication would be an event different from those known to re ult from the interaction of just two factors Thus we favor classifying the development of peptic ulcer during hormonal treatment of a patient with rheumatoid arthritis as a complication not a side effect on the assumption that that particular rheumatoid patient did provide the third factor namely the tendency to produce ulcers

But by the definition that a side effect is the result of overdo age in the disease under treatment an eventuality can be a side effect in one di ease

steroid (17 hydroxypregnanolone) which was absent from the urine of 30 normal persons but excreted by patients with disorders of adrenal function. Corticotropin was given to 1 of these patients. Excretion of the abnormal steroid was only moderately increased whereas that of the other recognizable adrenal hormone metabolites increased greatly.

It was concluded that adrenal dysfunction existed in these patients; that quantitative and qualitative alterations of production of hormone by adrenal glands are a significant feature of rheumatoid arthritis; are involved in the etiology of the disease; and may indicate "a primary defect which is followed by a long series of metabolic consequences terminating in a characteristic symptom complex."[347–351] Continuation of this work appears to us to be of considerable importance regardless of whether the alterations are related to the etiology or pathogenesis of rheumatoid arthritis or are primary or secondary in nature.

Undesirable Effects, Side Effects, Complications

Definitions. Writers sometimes discuss under one heading such matters as hormonal toxicity, sensitivity reactions, side effects, undesirable effects, physiologic effects, complications, even withdrawal reactions and, for good measure, pure coincidences or happenstances. It is even more common for physicians to put in a separate category the many physiologic effects a particular patient desires and to label all the others "side" or "undesirable" effects. Such distinctions may be arbitrary and artificial.

Another curious distinction has been made. Many workers have argued that the antirheumatic effect is a pharmacologic effect and that all the other hormonal results should be termed not side effects but physiologic effects. In other words, the good or desired effect is pharmacologic; the bad is physiologic. We agree with Selye and Horava[35] that the theorist cannot have it both ways at the same time.

For a clearer conception of hormonal action it is important to distinguish as far as possible between a physiologic effect, i.e., an undesirable one, from hormonal treatment and a complication of such treatment. Steinbrocker and associates[100] stated that they reserved the term "complications" for those "pathologic states developing during the administration of ACTH and cortisone which are not reversible after cessation of therapy or for those reactions which constitute a threat to the patient's well being or survival." Bilka and Cader[185] labeled as a complication "some disturbance whose exact relationship to cortisone is unknown."

Most writers have cautiously, perhaps wisely, refrained from distinguishing by definition between a physiologic and a pharmacologic effect, between a side effect and a complication. And yet our empirical use of the hormones can be improved only by making at least a beginning at such distinction, no matter how faulty the start may prove to be.

It is a matter of some practical importance to know which is a physiologic side effect and which is a complication. We do not believe one can try to define these two until one has first attempted to understand the presumed

back or abdominal pain hypotension and shock developed Patients responded to epinephrine and related drugs Such reactions should become increasingly rare as purified preparations become available

Hormonal Side Effects in Rheumatoid Arthritis As stated above, we believe a distinction should be attempted between hormonal side effects in cases of rheumatoid arthritis per se and complications in rheumatoid patients receiving hormonal therapy Thus the two main factors in the production of side effects in the rheumatoid patient are (1) the rheumatoid base line and (2) the dose or the patient s individual tolerance to dosage

THE RHEUMATOID BASE LINE Studies of side effects among rheumatoid patients should start from a special base line recognizing the various clinical and biochemical features of the untreated disease features which may either predispose rheumatoid patients to a specialized incidence of certain side effects or be mistaken for side effects

The following clinical features are characteristic of untreated rheumatoid patients and if their presence or absence is not specifically noted before hormonal therapy is begun their later discovery may be misinterpreted as a hormonal development when in fact they were preexistent but undetected either inflammatory or stasis edema (pitting or nonpitting) weakness fatigability exhaustion personality changes including marked depression [115 116] irregular menses sexual indifference or actual loss of libido

The following features of untreated rheumatoid arthritis may modify (increase or decrease) the incidence or character of side effects or may be mistaken for side effects diabetic like glucose tolerance curves easy bruising slight tendency toward a negative nitrogen calcium and phosphorus balance [135] osteoporosis in severe cases or in elderly rheumatoid patients hypotension and amyloidosis

HYPOTHETIC SIDE EFFECTS

Certain side effects which have been anticipated by others have never surely materialized permanent Cushing s syndrome permanent adrenal insufficiency permanent diabetes mellitus in a patient not already prone to diabetes increased incidence of atherosclerosis from hypercholesteremia and hepatic insufficiency from infiltration of fat Likewise corticogenic hypothyroidism—an entity which sometimes can be demonstrated by laboratory means in terms of decreased thyroidal uptake of radioiodine [2 207 361–366] lowered basal metabolic rate or decreased protein bound iodine [97 361 367] in the serum —has not been reflected clinically as a myxedematous state in any patient nor in our experience has it required or benefited from treatment with thyroid although others disagree [97 361 368]

OBSERVED SIDE EFFECTS AND COMPLICATIONS

The physiologic actions of cortisone and related hormones which directly or indirectly affect most if not all the systems of the body are considered in detail elsewhere in this book (Chapters 1 and 2) However it is appropriate here to mention briefly the clinical manifestations of hypercortisonism since

but a complication in another If this reasoning is valid there will be established in time not *one general list* of "hormonal side effects" as the matter is now usually treated but separate lists characteristic of each disease

We are not in a position as yet to differentiate between physiologic and pharmacologic effects or between side effects and complications, at least in many instances But to the extent that one has evidence or strong suspicion that a third factor has intervened, one is perhaps justified in listing certain untoward events as complications and not as side effects

Grouping of Untoward Events The various untoward events encountered during hormonal therapy of rheumatoid arthritis are (1) reactions to contaminants (2) allergic reactions (3) side effects definite or hypothetic (4) complications and (5) coincidences

Reactions Due to Contaminants or Diluents Rarely, a patient given cortisone intramuscularly has reacted unfavorably apparently not to cortisone per se but to the diluent to which the patient was sensitive [06] No such reactions have been reported from the oral use of cortisone

The newer more purified preparations of corticotropin appear to be essentially free from intermedin and other pituitary contaminants which earlier caused intestinal cramps flatus, pallor, and occasionally nausea vomiting or diarrhea and even transient localized pigmentation [9 35 23]

Allergic Reactions to Cortisone and Corticotropin Allergic reactions undoubtedly due to cortisone per se rather than to the suspending agent develop rarely [353] if at all No allergic or nonhormonal pharmacologic reactions to hydrocortisone have come to our attention

Sensitivity to corticotropin given intramuscularly has been reported in several rheumatoid and nonrheumatic patients [9 97 101 104 06 17 3 353–360] The more severe reactions occurred within 5 to 30 minutes after an injection of from 12 5 to 25 units or from later test doses of as little as 2 to 4 units [356] Any or several of the following developed vertigo pallor or flushing headache difficulty in breathing laryngeal edema urticaria angioneurotic edema hypotension and shock Patients responded to epinephrine Benadryl Pyribenzamine and related drugs Forsham reported acute anaphylactic shock after only three of about 10 000 intramuscular injections [06]

Subacute reactions sometimes developed a few hours or one or two days after the offending injection These consisted of either giant or small type urticaria and might be accompanied by fever Eosinophilia (1 000 to 4 000 cells per cc of blood) gradually developed after intramuscular use of one preparation and disappeared when another was used [23] Skin tests with various species of corticotropin gave positive results from only one or from all types of the hormone in different cases Desensitization was accomplished in 1 patient by giving repeated injections of very small gradually increased doses [356]

Although no acute reactions to intravenous use of corticotropin were noted among 60 patients by Forsham [06] a few severe ones have been reported among nonrheumatic patients [354 361] Within 15 to 20 minutes of injection headache nausea chill pallor generalized burning vomiting low

generally has been smaller than most of those tabulated These effects are cervicodorsal fat pad obesity of trunk with thin extremities, thin velvety skin telangiectases plethora, decreased or increased libido enlargement of salivary glands masking of signs and symptoms of infection polyuria, nocturia arterial occlusion, convulsions coma blurred vision ligamentous sprains, hypercholesteremia fatigability

Several typical rheumatoid patients have been found to have cells resembling those seen in lupus erythematosus in the peripheral blood at times when evidence of hypercortisonism (usually severe) has been present One or more of the following manifestations have frequently developed in such cases fever anemia leukopenia pleurisy pericarditis renal irritation and abdominal pain [146] We suspect that such reactions are not true lupus erythematosus in the usual sense but rather are lupus like reactions precipitated in some way by the effects of hypercortisonism in the rheumatoid patient no evidence of lupus erythematosus had occurred prior to the development of hypercortisonism in these cases and the reaction has disappeared slowly after elimination of hypercortisonism A few other rheumatoid patients with severe prolonged hypercortisonism have had transient histologic and clinical features simulating those of polyarteritis [146]

With greater experience some changes in the relative incidence of reported side effects are to be expected It is of interest to note that all the recognized manifestations of Cushing s syndrome except polycythemia have been observed as side effects in rheumatoid patients treated with cortisone or corticotropin

Incidence of Side Effects and Complications In general the reported incidence of side effects in different series of hormone-treated rheumatoid patients varies widely (Table 16) This is to be expected since so many factors are concerned particularly dosage duration of treatment type of case selected for treatment and the author s identification and tabulation of side effects

Dosage Dosage is the most important single factor influencing the incidence as well as the severity of side effects Authors agree generally that the larger the dose the greater the incidence of side effects We found that the incidence of side effects in a group of patients who received daily doses of 75 mg or more was three times as great as that observed in a similar group that received daily doses of less than 75 mg [7] Boland and Headley s[370] and Freyberg s[81] results were similar

Duration of Treatment The influence of the duration of treatment on the incidence of side effects is closely related to dosage Indeed the duration of treatment might be considered a permissive condition of the development of side effects An excessive dose may not become clinically apparent until it has been continued for some time Obviously a greatly excessive dose will cause hypercortisonism in a shorter time than a slightly excessive dose but even the latter eventually will manifest itself in the production of side effects On the other hand prolonged treatment without hypercortisonism can be accomplished by a schedule of dosage which is not excessive

their early recognition and prevention or treatment is so important in the management of rheumatoid patients receiving hormonal therapy Fortunately side effects develop gradually and, initially are usually mild and few in number If hypercortisonism is recognized in its early phase it can be readily and completely reversed by reduction or discontinuation of the dose of hormone Long-continued or progressive hypercortisonism may produce more serious consequences

Nature and Relative Incidence of Particular Untoward Effects The nature and relative incidence of some of the more commonly noted side effects and complications as recorded in a group of representative reports are listed in Table 15 [75, 81, 100, 107, 11, 229, 31, 59] In addition certain other effects or complications have been noted although to date their reported incidence

Table 15

NATURE AND RELATIVE INCIDENCE OF PARTICULAR UNTOWARD EFFECTS AND COMPLICATIONS MOST COMMONLY RECORDED IN REPRESENTATIVE REPORTS (510 PATIENTS TREATED)[75, 81, 100, 107, 112, 229, 231, 259]

Manifestation	*Patients*	*Manifestation*	*Patients*
Alteration in psyche	125	Decreased resistance to infection	8
Facial rounding	104	Headache	8
Fluid retention	96	Weakness	7
Hypertrichosis	46	Hypopotassemia	7
Decreased glucose tolerance	[illegible]	Neuropathy (especially neuritis)	[illegible]
Increased blood pressure	31	Disturbed renal function	6
Acne	25	Striae	6
Menstrual disorders	17	Aggravation of peptic ulcer	6
Tachycardia	16	Delayed wound healing	5
Supraclavicular fat pads	13	Thinning scalp hair	4
Ecchymosis or easy bruising	13	Arteritis	3
Increased sweating	12	Pigmentation	3
Excessive appetite or gain in weight	11	Fractures (osteoporosis)	[illegible]
Thrombophlebitis	10	Temporary pituitary adrenocortical suppression	1
Aggravated menopausal symptoms especially hot flushes	9		

* Recent data indicate that there is a much greater incidence of this effect

generally has been smaller than most of those tabulated. These effects are cervicodorsal fat pad obesity of trunk with thin extremities thin velvety skin telangiectases plethora decreased or increased libido, enlargement of salivary glands masking of signs and symptoms of infection polyuria nocturia arterial occlusion convulsions coma blurred vision ligamentous sprains hypercholesteremia fatigability

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This explains why the incidence of side effects may not increase greatly and even may diminish after the first few weeks or months of treatment [229,231, 9]

Plan of Treatment This factor is simply the resultant of the two preceding factors, dosage and duration of treatment Short courses of treatment

Table 16

REPORTED INCIDENCE OF SIDE EFFECTS AND COMPLICATIONS

Series	Patients	*Side Effects (Percentage of patients)*		*Average Daily Maintenance Doses*		*Duration of Treatment*
		Mixed (minor and/or major)	Major	Cortisone (mg)	Corticotropin (units)	
Ward and co workers[229]	46	20	0	50		15 mo (av)
Bilka[185,186]	36	25	?10	Less than 100		1 wk –5 mo
Boland[231]	60	40	2.5	37.5–80.5		10 mo (av)
Davison [2]	19	47	?26	100/wk – 100/day		Not stated
Margolis[269]	56	50	?23	Not stated	30–120 initial then reduced	7–225 days
Ward and co workers[76]	100	54	7	25–100		1–12 mo
Kuzell and Schaffarzick[7]	19	65	53	50–75		62 days (av)
Levin [59]	50	88	?52	75–80	47	1.5–8 mo
Ragan[60]	59	?100	?36	Doses to induce hyperadrenalism		10–12 mo
Chase [94]	7	100	86	Massive (up to 800)		18.8? days

with a given dose may produce fewer clinical manifestations of hypercortisonism than would longer periods of treatment with the same dose Yet some of the highest incidences of side effects have been reported in patients given brief courses of treatment with high doses [189–191, 94] Thus the incidence of side effects from the interrupted course method of treatment may be high or low depending upon the size of the doses and duration of treatment just as the incidence in prolonged treatment may be high or low depending upon dosage

Age Children have a greater tendency to develop side effects than have adults Elderly men seem to tolerate cortisone or corticotropin about as well as do younger men, and elderly postmenopausal women seem to be no more susceptible to hypercortisonism than are younger postmenopausal women

Sex and Menopause Women in general are more likely to have side effects than are men [9, 5, 60, 231, 371] likewise menopausal or postmenopausal women tend to develop side effects more readily than do premenopausal women [75]

Severity of the Disease We have had the impression that in many cases the more severe the rheumatoid process the greater the tolerance for cortisone Unfortunately the increased tolerance apparently does not always keep pace with the dose necessary to control the increased severity of disease since the more severe disease tends to be less well controlled with safe doses of the hormones [80, 100, 107, 11, 59, 370]

Complicating Conditions An increased incidence of complications from hormonal therapy is to be expected if the series of treated rheumatoid patients includes those with other conditions susceptible to aggravation by cortisone or corticotropin e g hypertension congestive heart failure renal insufficiency quiescent tuberculosis peptic ulcer diabetes or marked osteoporosis

Hormone Used Side effects produced by cortisone hydrocortisone and corticotropin are essentially similar in nature However certain quantitative differences have been reported in some cases Thus corticotropin has been said to produce more retention of sodium and water more potassium depletion more acne and hirsutism more pigmentation more changes in arterial pressure, but a shorter period of relative adrenocortical insufficiency following cessation of hormonal treatment [101, 109, 171] Boland [3] has reported a lower incidence of side effects among patients treated with hydrocortisone than among those treated with cortisone acetate especially in regard to edema nervous symptoms, facial fullness and supraclavicular fat pads [76, 109] Our less extensive experience with hydrocortisone has not revealed a significant difference in the incidence of side effects from cortisone and hydrocortisone the discrepancy in results in Boland's[109] and our series may be related to differences in doses employed

Death of Rheumatoid Patients during or after Hormonal Therapy References have been found to 32 rheumatoid patients who died from various causes during or some time after conclusion of treatment these are not represented as complete Of these 32 deaths 9 (28 per cent) were definitely or probably related to treatment The relationship of the other 23 (72 per cent) was either possible but doubtful entirely coincidental or not clear

Relationship Definite The most important and common cause of death was acute postoperative adrenal insufficiency in patients who underwent operation during or after hormonal treatment while their adrenocortical reserve function was still inadequate Four such cases have been reported [154, 155, 157, 164, 194, 372] The regimen for the prevention of such accidents is described on page 251 Another patient committed suicide during acute

psychosis [374] In the light of present knowledge such deaths as these can be prevented

Relationship Probable In 4 cases, hormonal therapy was probably a major factor But details are meager in 2 cases mentioned by Sokoloff and associates,[147 163] in each of which both cortisone and corticotropin had been given One of these patients died of status epilepticus 38 days after administration of corticotropin and 19 days after administration of cortisone had been discontinued the other died of fulminating pneumonia (during or after hormonal treatment) 'masked clinically or potentiated by ACTH' [374]

A 57 year old woman who had virulent progressive rheumatoid arthritis "extreme cachexia' anemia and fever received cortisone for 87 days then corticotropin for 22 days Eight days after this treatment was discontinued hematemesis developed from a chronic gastric ulcer, and she died four days later [113]

A male baby receiving cortisone for rheumatoid arthritis had slight fever and vomited twice next day he died within an hour in a state of tonic convulsion of the jaw with dyspnea and cyanosis' Necropsy revealed "a thymus rather larger than normal for his age [unstated] and a brain rather more edematous than that usually found following a convulsive death' Cause of death was not determined [71]

Relationship Possible A 61 year old patient died apparently from cardiac failure 33 days after his last dose of cortisone (6 6 Gm in 39 days), another patient with bronchiectasis had an overwhelming pulmonary infarct [80]

Relationship Unknown The connection between 7 deaths and hormonal therapy cannot be determined In 4 of these the hormone was not identified and in 5 time relationships between treatment and death were not stated [80 147 163 59] Hydrocortisone injected into a joint has resulted in convulsion and death in 1 patient according to Kern [52] no other details were given

Coincidental Deaths Fourteen deaths considered coincidental resulted from acute coronary disease in 5 cases [9 10 331] apoplexy in 3 [80 95 113 31] and miscellaneous causes in 6 cases [6 86 163 193 375]

PREVENTION AND TREATMENT OF SIDE EFFECTS AND COMPLICATIONS

Careful selection of cases and proper regulation of dosage are generally regarded as the most important factors in prevention and treatment of side effects and complications Certain supplementary measures also have been useful particularly in controlling some side effects that may develop during the period of establishing a maintenance dose [81 101 206 9 376 377] These in brief, are restriction of intake of sodium to 0 5 to 2 Gm per day and if necessary for fluid retention use of diuretics such as potassium chloride or nitrate 1 to 2 Gm three times daily or mercurial diuretics for hypopotassemia potassium chloride 1 to 2 Gm three times daily, for insomnia or other manifestations of mild mental stimulation reduction of dose of the

hormone at the appropriate time e g at bedtime or use of sedatives such as barbiturates or chloral hydrate, and for aggravated menopausal symptoms estrogens such as Premarin 1 25 to 2 5 mg per day If diabetes is present management with dietary measures and insulin may need to be intensified Patients who have had a peptic ulcer should follow a careful dietary and antacid regimen during treatment with cortisone even though the ulcer has been quiescent for some time Patients with significant degrees of osteoporosis should be warned against sudden increases in traumatic activity e g unusual lifting in order to avoid fractures Patients who tend to gain weight excessively must limit caloric intake sufficiently to keep their weight at the desired level The tendency toward production of a negative nitrogen balance can be counteracted at least in part by liberal intake of nitrogen e g a 120 to 200 Gm protein diet Testosterone and a high intake of potassium also have been said to be helpful in this regard [376–378] The use of a high fat–high protein–low carbohydrate diet has been advocated by Kinsell[376 377] as a help in reducing the incidence and severity of side effects generally Appropriate chemotherapeutic or antibiotic agents should be administered if intercurrent infections develop The prevention and management of complications arising from increased stress or upon withdrawal of hormonal therapy are discussed on pages 250 and 238

Coincidences and Happenstances

Unfortunate accidents or complications unrelated to treatment will inevitably befall some patients undergoing therapy for rheumatoid arthritis purely on the basis of chance Yet these coincidences or happenstances have been improperly attributed to the effects of therapy in some instances This has been particularly true when angina pectoris myocardial infarctions cerebrovascular accidents and miscellaneous conditions developed in patients treated with cortisone One of our rheumatoid patients died from coronary insufficiency two days before treatment with cortisone was to start another exhibited thrombophlebitis one day prior to the planned institution of systemic therapy with hydrocortisone These fortuitous happenings might have been attributed by some to the effects of the hormones had treatment been started a few days sooner

Conclusions Regarding Side Effects

Side effects should be respected but not feared In properly managed cases they are of more significance as factors which limit achievement of the maximal antirheumatic response than as conditions harmful in themselves although they may become harmful if allowed to persist or progress Side effects are reversible and transient usually develop slowly and rarely present an emergency to the alert physician therefore manipulation of dosage usually can be deliberate Some physicians sensitized to potential therapeutic hazards forget or underestimate the ever threatening side effects of rheumatoid arthritis itself a disease that involves distress and fearsome hazards which fully justify calculated risks (Figure 28)

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causing a corresponding increase in side effects These substances are adenosine triphosphate[388] ascorbic acid[389] allopregnane 21 ol 3,20 dione,[114] glucuronic acid,[418] gold salts,[18] gonadotropins,[183] insulin[419 4 0] p-amino benzoate,[388 421] pregnenolene[385] salicylates streptococcus vaccine[4 2] sulfosine,[423] testosterone[385] and vitamin E[388]

Table 17

TESTED AS SUBSTITUTES

21 Acetoxypregnenolone[1 3 9 380]
Adrenocortical extract[6]
  Lipoadrenal cortex extract[1]
  Concentrated adrenocortical extract
Adrenal implants[351]
Adreno nephro-colopexy[2]
Allopregnane-3β 21 diol 20-one[114]
Allopregnane-21-ol 3 20-dione[114]
Androstenedione[38]
Anesthesia of glomus caroticum[3]
Anhydrohydroxyprogesterone[85]
6-Bromocortisone[60]
Δ^5 Cholene 3β 25-diol[7]
Chorionic hormone[386 3]
Corticosterone (Kendall s compound B) (unpublished data)
11 Dehydrocorticosterone (Kendall s compound A)[6]
$\Delta^{16\ 17}$ 11 Dehydrocorticosterone
6 7 Dehydrocortisone[16 49]
Dehydroisoandrosterone[79 8 388]
11 Desoxycorticosterone[16]
  Desoxycorticosterone and ascorbic acid[304 89]
  Desoxycorticosterone and methylene blue[3]
21 Desoxy 11-dehydrocorticosterone[6]
4 5 Dihydrocortisone
Dihydroergotamine
Epinephrine[3 8 2 3]
  l Epinephrine[39]
  Norepinephrine[392]
16 17 Epoxy 11-dehydrocorticosterone[5]
Ergostanyl[395]
Estrogens[379 387]
Growth hormone[39]
17 Hydroxy 11-desoxycorticosterone (Reichstein s compound S)[16 4 397]
3 Hydroxy 2 phenylcinchoninic acid[3 8 393]
17 Hydroxyprogesterone[16 3 7]
Irradiation (radar and roentgen) of hypothalamic region[4 401]
Insulin hypoglycemia[3 4 2]
Isoandrostenolon[8]
11 Ketoprogesterone
Licorice extract[4]
d Methorphinan[405]
17 Methyl Δ^5 androstendiol 3β 17[6]
Pituitary implants[406 07]
Placental extract[08]
Placental serum[0]
Placental tissue implants[9 410]
Posterior pituitary extracts[41]
Postpartum plasma[412]
Pregnadienolone[114 85]
Pregnancy blood[8]
Pregnane 3 12 20 trione[39]
Pregnant mare serum[38]
Δ^5 Pregnenolone[16]
Pregnenetriolone[97]
Progesterone[254 3 9 8 3]
Salicylates[414– 6]
Testosterone propionate[379 417]
  17α allyl testosterone
  Methyltestosterone[3]

The antirheumatic activity of some specially prepared highly concentrated adrenocortical extracts can be accounted for by the content of cortisone like hormones probably largely hydrocortisone[16] Otherwise none of the many substances tried has been found to be a consistently effective substitute for or potentiator of the hormones cortisone hydrocortisone, or corticotropin despite some favorable initial reports

Supposed Mode of Action

The basic mechanism whereby cortisone and corticotropin exert their antirheumatic effect is not known These agents generally have been supposed to protect certain tissues from noxious agents in some obscure way perhaps by interposing a shieldlike buffer between the tissues and the injury

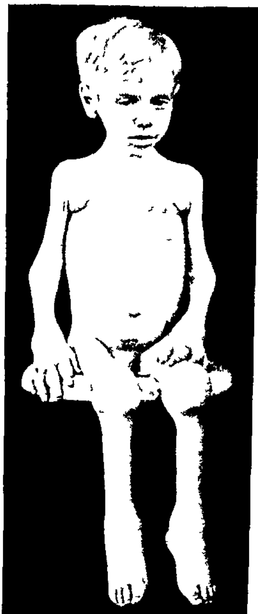


Fig. 28. Side effects of progressive rheumatoid arthritis. The physician in his laudable concern over the side effects of therapy, whether with gold salts, hormones or other agents, must never forget the distressing side effects of uncontrolled progressive rheumatoid arthritis.

Substitutes or Potentiators

In an attempt to find substitutes which would be more readily available or produce fewer undesirable physiologic effects, many substances and methods of treatment have been tried. Some of them are listed in Table 17.[378–417] Also, various substances have been employed in efforts to potentiate the antirheumatic effects of small doses of cortisone and corticotropin without

Table 18

DEVELOPMENTS AFTER DISCONTINUANCE OF TREATMENT WITH HORMONES BY THE COURSE METHOD (PLAN 1)

Posthormonal Development	*Our First Series of 23 Patients Treated Doses High Usually Were Reduced and Discontinued Abruptly (Percentages)*	*Representative Reports of Others 1950–1952 Total Doses for Courses Smaller Doses Sometimes but Not Always Reduced Gradually (Percentages)*
I Articular Remission prolonged more or less complete (7–14 mo)	13	0–12
Secondary remission	8	Instances reported with out statistics
Partial remissions incomplete but notable Return of arthritis unusually slow (2–3 mo)	4 = 1 patient (50 per cent relief after 5 mo)	Variable (20–45) depending on definition of partial remission
Fairly prompt return of pretreatment symptoms (in 1 week to about 2 mo)	66	46–83
Rebound arthritis — marked	9	3–12†
Total	100	
II Systemic withdrawal symptoms No significant reaction	48	Common
Mild or moderate reaction	48	Frequent
Marked	4	4‡
Total	100	

0 [2] 3 per cent [9] 4 per cent 5 per cent [185] 12 per cent [2]
† 3 per cent 4 per cent [5] [86] 6 per cent [7] 7 per cent [8] using Astwood s corticotropin— rebound attacks only 2 to 3 days long 12 per cent [73]
‡ Bilka 1952 [2]

pregnancy or jaundice 4 In a few cases a brief relapse has been followed by a secondary remission with notable but often incomplete relief lasting as long as several months in some instances 5 Articular rebound attacks have developed promptly in a few patients joints and muscles becoming affected quickly and severely Sometimes they become temporarily worse than ever

Withdrawal Reactions Obvious withdrawal reactions may not occur (1) if the hormones have been given carefully in doses—and for periods—that

or by modifying the reaction of tissues to injury [61,115,116,434] Various hypotheses as to how this protection is afforded have been offered by interfering in some way with antigen antibody reactions or other allergic phenomena [175,435] by supplying a relative deficiency of hormones to the tissues [61] by influencing enzyme systems[53,92,426–428] or cellular permeability,[25,53,425] by decreasing the activity of connective or mesenchymal tissue, [345] by suppressing mitosis,[4 [illegible]] or by decreasing the sensitivity of tissue to a mineralo corticoid type of response [35] But the statement made by Kendall[50] on the occasion of his Nobel lecture in 1950 still applies '*What physiologic processes are modified by cortisone and how this influence is exerted are matters still locked within this hormone of the adrenal cortex*

Developments after Discontinuance of Hormonal Treatment

The developments which occur after discontinuance of hormonal treatment can be divided into two main groups those which concern only the disease i e, relapse or remission of rheumatoid arthritis and those related to physiologic disturbances caused by the previous treatment i e withdrawal reactions After withdrawal of the hormone, a given patient may present features reflecting not just one of these disturbances but a composite of rheumatoid articular relapse, acute or subacute hypocortisonism and residues of hypercortisonism

Rheumatoid Response When a course of treatment has ended rheumatic symptoms usually return rather promptly but sometimes their return is slow occasionally very slow

General Pattern of Relapse Generally within one to eight weeks muscular and articular stiffness reappears fever may return appetite begins to diminish energy is replaced by the usual fatigue and weakness and the E S R begins to increase Next articular aching, tenderness and pain on motion recur, then articular swelling reappears More slowly the following may return if they have been present before treatment anemia loss of weight characteristic alterations in serum proteins enlargement of lymph nodes and subcutaneous nodules and perhaps flexion deformities As a rule, symptoms return a little later (sometimes a week or so) after the intramuscular use of cortisone (because intramuscular "pools" thereof may continue to be absorbed slowly) than after the oral use of cortisone or the intramuscular use of corticotropin

Difference in Speed and Intensity of Rheumatoid Relapses Some Prolonged Remissions After a course of hormonal treatment has ended the rheumatoid patient may experience any of the following results (Table 18) 1 A prompt relapse usually occurring in about one to eight weeks is most common and affects one-half to three fourths of the cases 2 Slowly fading remissions are the next most common reaction Symptoms return slowly and gradually giving the patient a partial but welcome remission for three to five months or more 3 A rather prolonged remission has occurred in some instances This desirable result generally develops haphazardly and as unpredictably as spontaneous remissions or the occasional lengthy ones after

Systemic Reactions Related to Hypercortisonism The effects of any previous hypercortisonism (in addition to pituitary adrenal suppression), e g the disturbances in metabolism of electrolytes proteins fat and carbohydrate may require days or weeks for correction after treatment is discontinued Hence during that time the effects of residual hypercortisonism are superimposed on those of the acute or subacute hypocortisonism

Onset Duration and Severity Symptoms usually begin within a few hours or days after withdrawal of hormonal treatment although in a few instances systemic reactions have been delayed for as long as two to five weeks [9] The reactions which occur in all gradations of severity from mild to marked may persist for a few days or up to three months rarely longer This approximates the duration of pituitary adrenocortical suppression The longer the existence of hypercortisonism during treatment and the greater its degree at the time of withdrawal generally the more severe and prolonged the reaction Thus the incidence and severity of withdrawal reactions can be expected to be less in patients treated with relatively short courses and with doses that produced little or no hypercortisonism than in patients who were treated at length with excessive doses although the general nature of the reaction may be the same in both groups

All the components of the withdrawal reaction tend to subside gradually but often the objective evidences of hypercortisonism disappear first the musculoskeletal reaction next and the systemic reaction of hypocortisonism last

Prevention Withdrawal reactions at present must be considered to result at least to a great extent from disturbances in physiology created by previously induced pituitary adrenocortical suppression and exogenous hypercortisonism Three suggestions based upon theoretic considerations and upon their value in actual practice are offered for the prevention or lessening of these reactions

(1) Regulate dosage properly during treatment to prevent hypercortisonism and as much as possible pituitary adrenocortical suppression (although to date the relation between dosage and pituitary adrenocortical suppression is not completely defined)

(2) Reduce the hormone gradually rather than abruptly For example in the case of a patient who has been receiving 40 mg of cortisone or corticotropin the dose might be reduced by decrements of 2 5 or 5 mg every few days if necessary This allows the patient to adjust reasonably well to the previous dose reduction before the next decrement In general the higher the dosage and the longer the treatment the longer the period required for tapering the dose

(3) Use short courses of treatment whenever indicated Patients who have been treated for less than four to six weeks usually do not have clinically significant withdrawal reactions Unfortunately however such short courses usually are not satisfactory in the management of most rheumatoid patients

Treatment The prevention or lessening of symptoms by the measures just considered is the primary consideration in management of withdrawal

are insufficient to produce significant or recognizable hypercortisonism or pituitary adrenocortical suppression or (2) if withdrawal has been slow enough to permit considerable restoration of pituitary adrenocortical function before the last dose In such cases rheumatic symptoms and increased E S R 's return to but do not exceed their pretreatment status i e rebound arthritis does not occur No muscular weakness or fatigue becomes apparent either as a carry over from hypercortisonism or from cortical suppression although the usual rheumatic weakness and fatigue commonly return

In contrast certain patients to whom the hormones have been given less carefully may experience on withdrawal of the hormone a group of reactions which seem related in great part to physiologic disturbances created by previous hormonal therapy The reactions can be divided into three main groups (1) musculoskeletal reactions (2) reactions related to hypocortisonism and (3) reactions related to residual hypercortisonism

Dissociation between the various developments which comprise the withdrawal reaction may be marked In 1 patient the latter may be chiefly musculoskeletal i e rheumatic in another systemic in a third a combination of musculoskeletal and systemic responses and in a fourth asymptomatic but demonstrated by such findings as a rebound increase in the E S R to a level higher than it was before treatment rebound eosinophilia mild hypotension or changes in excretion of steroids or in levels of serum electrolytes

Etiology More information is needed concerning the pathologic physiology of the reaction However one of the main factors in its occurrence seems to be hypocortisonism resulting from temporary suppression of pituitary-adrenocortical function induced by administration of these hormones as discussed previously In addition to the manifestations of hypocortisonism residual manifestations of hypercortisonism, if any exist in the particular case also temporarily exert their effect upon the metabolic processes However parts of the reaction particularly the musculoskeletal phase, seem to require conditioning by the underlying rheumatic process since similar musculoskeletal reactions are unusual in patients who have not had a rheumatic process such as rheumatoid arthritis or lupus erythematosus

Musculoskeletal Symptoms The symptoms of the musculoskeletal withdrawal reaction need to be and usually can be differentiated from the symptoms of a true rheumatoid flare The former bear a striking resemblance to the pseudorheumatism of hypercortisonism

Systemic Reactions Related to Hypocortisonism following Withdrawal of Hormones These may consist of muscular weakness lassitude fatigue, exhaustion prostration fever anorexia nausea vomiting abdominal cramps diarrhea diuresis dizziness, headache mental depression or irritability hypoglycemia exaggerated increases in E S R or eosinophil counts changes in steroid excretion retention of potassium and loss of sodium and chloride Various combinations of these symptoms may be present in almost any degree of severity

Program 2 Hormonal Therapy From cortisone or corticotropin relief is generally prompt and marked and can be effectively maintained by continued treatment in at least 50 per cent of cases The cost of maintenance doses of cortisone although still high is now less than the cost of gold salts plus the necessary weekly laboratory examinations required during chrysotherapy it is also less costly than the expense of professional physical therapy given two or three times a week Potential side effects comprise the chief objection to the use of this program These prevent the continued use of hormones in about 15 per cent of cases and necessitate the careful use of suboptimal doses in about 35 per cent But if patients are managed carefully at least 50 per cent may attain satisfactory antirheumatic results without side effects When transient side effects occur they are certainly no more troublesome indeed usually less so and are more reversible than those from gold salts

Program 3 Chrysotherapy If gold salts work significant relief usually develops in weeks not hours or days as from cortisone, but if remissions are induced the relief after chrysotherapy is stopped may last longer than that after hormonal therapy Toxic reactions to gold salts are still common and occasionally serious But most important an average of only about 15 per cent of patients given gold salts have developed marked relief comparable to that which hormonal therapy commonly and rather promptly affords [439]

Treatment of Choice There is no one treatment of choice for the disease but there is commonly a treatment of choice for the patient Program 1 General Measures is the choice for early mild or nonprogressive rheumatoid arthritis according to most physicians Even when it is inadequate by itself as is often the case Program 1 should be continued in conjunction with whatever other forms of therapy are added We and many others are of the opinion that Program 2 Hormonal Therapy unless contraindicated by complicating conditions is the choice in patients for whom Program 1 alone does not suffice We use Program 3 Chrysotherapy for patients who are not suitable for treatment with hormones either because of complicating conditions or because previous experience has shown them to be unduly susceptible to the adverse effects of such treatment Others prefer to employ chrysotherapy before cortisone [437, 438, 440, 441] One physician prefers gold salts in cases of less than one year s duration cortisone in the others [66]

Whether the combined use of hormones and gold salts offers any advantage remains a disputed question [66, 5, 19, 44] Some have advocated their concomitant use in order to obtain the quick benefits from cortisone while awaiting the more delayed benefits from gold Others have considered that the combined use enables the more rapid administration of larger doses of gold salts [431] Some[19] but not others[186, 443] have concluded that gold potentiates cortisone which then can be used more effectively in smaller doses Some have reported that the continued use of gold after discontinuance of treatment with hormones prolongs the hormonally induced remission [369] others disagree [69, 89, 431] Combined use of hormones and gold salts may be considered for severe arthritis which requires more relief than the use

reactions However if withdrawal symptoms do occur, certain measures are helpful

(1) Most of the mild or moderate withdrawal reactions can be treated symptomatically Even severe reactions can be helped by simple supportive measures such as increased rest—even hospitalization for severe reactions—replacement therapy in case of electrolyte disturbances and the use of simple analgesics such as aspirin 2 6 to 5 2 Gm daily physical therapy and appropriate supports or splints for musculoskeletal symptoms

(2) For some severe withdrawal reactions temporary resumption of hormonal therapy may be necessary One should repeat approximately the previous maintenance dosage long enough to control the reaction Thereafter the dose may be reduced more gradually than it was previously, e g by decrements of 2 5 to 5 mg every week or so Many physicians have the clinical impression that withdrawal reactions sometimes seem briefer and less severe after corticotropin than after cortisone although this impression has not been demonstrated certainly as yet Therefore, for some patients previously treated with cortisone corticotropin may be tried instead either by the method of gradually tapered intramuscular doses, or by intravenous administration (10 to 20 units in eight hours)[201] for a few days until an adrenocortical reactivation is evidenced by a clinical response

Our Policies, Practices and Recommendations

Comparison of Hormonal Treatment with Other Measures

Cortisone hydrocortisone and corticotropin are now considered practical useful agents in the treatment of selected cases of rheumatoid arthritis by most investigators [65 95 96 100 103 111 115 116 182 193 212 5 2 7 9 3 3 8 377 4 5 430–438] However opinions differ widely as to the type of case in which such treatment is appropriate Some physicians limit hormonal therapy to a 'small proportion' of cases[115 116] or to rapidly worsening conditions[69] or use it only 'when other treatments have failed' [79] others consider it "the most satisfactory single therapeutic agent now used in rheumatoid arthritis [2 5] Spies and associates[106] concluded that ' the judicious use of these hormones requires a great deal of scientific information yet it is desirable that physicians in practice use them With this we agree

Alternative Measures Omitting modifications and embellishments there are, in our opinion only three noteworthy programs of medical treatment for rheumatoid arthritis These are

Program 1 General Measures These include analgesics physical therapy reduction of articular trauma extra rest proper nutrition and other supportive measures This program may suffice for some cases of early mild or nonprogressive arthritis Unfortunately it is inadequate in many cases not only because many patients are not conscientious in the application of these measures but also because too often this program may not afford sufficient symptomatic relief and may fail to halt or delay the progress of the disease

Program 2 Hormonal Therapy From cortisone or corticotropin relief is generally prompt and marked and can be effectively maintained by continued treatment in at least 50 per cent of cases The cost of maintenance doses of cortisone although still high is now less than the cost of gold salts plus the necessary weekly laboratory examinations required during chrysotherapy it is also less costly than the expense of professional physical therapy given two or three times a week Potential side effects comprise the chief objection to the use of this program These prevent the continued use of hormones in about 15 per cent of cases and necessitate the careful use of suboptimal doses in about 35 per cent But if patients are managed carefully at least 50 per cent may attain satisfactory antirheumatic results without side effects When transient side effects occur they are certainly no more troublesome indeed usually less so and are more reversible than those from gold salts

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general measures plus either gold or hormones can provide However this plan should not be applied as a "shotgun" mixture but only on the basis of careful selection and knowledge of the patient's response through previous application of each of these measures separately

In the choice of treatment we have a great responsibility to the patient and we must be objective not personal have an opinion but not be opinionated In the care of the rheumatoid patient we must not be chrysotherapists cortisonologists, or physiatrists alone but rather physicians or rheumatologists using whatever will be of benefit As physical therapy and chrysotherapy help many patients, we must use them, as hormones help many we must learn to use them better and better If a patient's condition is equally suitable for chrysotherapy or hormones he should have first that which his physician can give with greater skill and confidence Such is the chronicity of this disease that whatever remedy is used first, many patients may have time and need for the other remedy later

Practicability of Hormonal Therapy of Rheumatoid Arthritis as an Office Procedure Hormonal therapy is now practicable as an office procedure for most general practitioners or internists and all rheumatologists, if the physician follows certain requirements These are (1) a reasonable familiarity with the physiologic effects of the hormones and with the disease (2) careful selection of patients (3) careful management which involves the willingness or ability to allow sufficient time for each follow up consultation e g 15 to 30 minutes (4) an alertness to detect incipient manifestations of hypercortisonism by clinical appraisal and (5) the recording of certain data The recording can be accomplished by means of a simple running tabular chart designed to show the date of each consultation hormone used daily dose and its division patient s weight and blood pressure brief numerical grading of the changeable tenderness swelling and range of motion of three or four representative key joints nature and severity of side effects if any and measures taken to eliminate them, results of laboratory tests

Actually the use of these latest hormones presents to the physician no strange new problem rather it is an old familiar problem of being able to balance the beneficial effects of a hormone or any other medicine against the possible undesired effects Any physician who can manage diabetic patients with insulin or rheumatoid patients with gold salts can learn to use cortisone or corticotropin with reasonable safety He should be able to give superior if not yet complete relief to at least half of his rheumatoid patients whom he selects and treats wisely

Answer to Criticisms and Objections to Use of Hormones The use of the hormones in treatment of rheumatoid arthritis has been subjected to criticism by some physicians for various reasons most of which are no longer valid

(1) Costliness and limited availability—The pharmaceutical industry has solved these problems so that the hormones are available in any desired quantity and at a cost no greater than that of many other medicines

(2) Transient, noncurative action requiring prolonged administration

and permitting the underlying disease to persist—A similar objection could but should not be raised concerning the use of insulin for diabetes liver extract for pernicious anemia or digitalis for congestive heart failure

(3) Unknown or pharmacologic (irrational) rather than physiologic (rational) mode of action—This gap in knowledge also true of many other forms of treatment should be more of a challenge to the investigator than an objection to the careful clinical use of these substances

(4) Worsening after stopping of treatment—Proper management during treatment and withdrawal eliminates or minimizes this development

(5) Occurrence of undesired effects—As discussed in the preceding pages this is one of the greatest limiting factors in the achievement of maximal antirheumatic results but side effects themselves can be controlled as described on page 234

Our Present General Policy of Hormonal Administration

Our present general policy with regard to use of these hormones in treatment of rheumatoid arthritis is to administer doses which will give optimal not necessarily maximal antirheumatic results the greatest relief that can be obtained without the development of side effects Until more is known about these hormones about pituitary and adrenocortical function in rheumatoid arthritis and about the control of side effects we cannot expect to achieve complete suppression of rheumatic symptoms for indefinitely prolonged periods in most cases

Selection of Patients Qualifications which we require for hormonal treatment are as follows (1) an active rheumatoid process i e one potentially responsive to hormonal therapy (2) failure to respond adequately to a fair trial of general measures (Program 1) (3) psychologic suitability—i e the patient must be capable of sustained cooperation despite the fact that treatment will be prolonged that it is suppressive rather than curative is variably effective from time to time and will require close supervision and probably various dose changes including at times reduction of dose because of side effects and despite incomplete control of symptoms and (4) absence of absolute contraindications to the use of hormones In the presence of relative contraindications the possible benefit from treatment must exceed the increased risk presented by the complicating condition

Contraindications to Use of Hormones Certain conditions which may be aggravated by cortisone hydrocortisone or corticotropin provide contraindications either relative or absolute to the hormonal treatment of rheumatoid arthritis (Table 19) The reasons for including the conditions listed in Table 19 as contraindications are readily apparent on consideration of the known physiologic activities of the hormones Another important contraindication of a different nature is the lack of a definite indication for the use of the hormones

In our opinion the use of cortisone if needed may be undertaken cautiously at present for rheumatoid patients who have certain conditions previously listed by some as absolute contraindications pregnancy,[444]

previous myocardial or cerebral infarctions,[445, 446] arteriosclerosis,[447] angina pectoris, hirsutism [448] properly treated syphilis,[206, 447] chronic hepatic disease, [57] senescence [49] cardiovascular abnormalities [57] of minor degree in patients more than 50 years of age, decubital ulcers, [39] debility,[49] and surgical procedures [445] Rheumatoid patients commonly obtain spontaneous relief during pregnancy Therefore the continued use of cortisone is generally not required during pregnancy But for patients not beneficially affected after two or three months of pregnancy it is apparently safe to use the hormones in moderate doses [449–451] We try to avoid their use during the first two or three months in view of the experimental production of developmental abnormalities in fetuses of certain animals by excessive doses of cortisone [449, 452–4 s] to date however, these anomalies have not been observed in human beings and limited clinical experience suggests that moderate doses may be employed safely even in the first trimester of pregnancy

Table 19

PRESENT CONTRAINDICATIONS TO USE OF HORMONES IN RHEUMATOID ARTHRITIS

Absolute
1 Tuberculosis active or recently active (within preceding 5 years)
2 Psychosis
3 Cushing s syndrome
4 Serious infections in which organisms cannot be controlled readily by antibiotics e g viral infections such as acute poliomyelitis
Relative
5 Other severe or moderately severe infections
6 Renal insufficiency
7 Peptic ulcer
8 Severe psychoneurosis or history of psychosis now in remission
9 Osteoporosis
10 Diabetes mellitus
11 Cardiovascular insufficiency including myocardial insufficiency hypertension and tendency to thrombotic or thromboembolic phenomena
12 Convulsive disorders

Future advances in medicine eventually may permit extension of the usefulness of cortisone in the presence of certain conditions now considered contraindications For example, recent studies suggest that adequate amounts of streptomycin may successfully counteract the enhancing effect of the hormones upon tuberculosis Likewise for some patients who have bacterial infections for which appropriate antibiotic therapy is available the supplemental use of cortisone has been said to be of great therapeutic value [57]

Examination of the Patient Prior to hormonal treatment the complete medical history should be obtained and physical examination performed Details of the past course and present condition of the arthritis should be noted carefully The usual laboratory tests urinalysis erythrocyte and leukocyte counts, determination of hemoglobin and E S R serologic test for syphilis, and roentgenograms of the thorax and appropriate joints should

be made Attention should be given to the possible presence of any complicating conditions that might be aggravated by the hormones Special laboratory tests for such conditions should be employed as necessary, e g , a fasting blood sugar if there is a history of diabetes in the family, a roentgenogram of the stomach and duodenum if the history is suggestive of peptic ulcer determination of blood urea if renal insufficiency is suspected

During treatment the patient should return periodically for supervision For the first few weeks these visits should be made every two or three days then at intervals gradually lengthened to every two to four weeks if progress is satisfactory Complications such as articular flares intercurrent illness or hormonal side effects may necessitate additional return visits At each visit the antirheumatic response should be noted carefully evidences of side effects or complications should be sought, and the dose of hormone should be adjusted if necessary The patient should be weighed each time Urinalysis should be performed at the end of the first week of treatment then at intervals of one to two months Blood pressure should be taken at monthly intervals or oftener if the patient is hypertensive Determination of E S R hemoglobin and leukocyte count should be obtained every three to six months Roentgenograms of the thorax should be repeated every 6 to 12 months More frequent or additional tests should be performed as indicated by the circumstances of the case

In the past considerable attention was given to various laboratory tests, e g , frequent determinations of eosinophil counts serum electrolytes E S R or urinary excretion of steroids as possible guides to regulation of dosage These and many other tests have provided useful information for purposes of research However it is now generally agreed that laboratory tests cannot replace careful clinical appraisal as the principal basis for management [66 97 100 109 2 9 304 459]

Choice of Hormone Either cortisone hydrocortisone or corticotropin can be used effectively We have given cortisone acetate by the oral route in most cases primarily because of convenience of administration Whether the use of hydrocortisone (free alcohol) instead of cortisone acetate offers any significant advantage requires further study

Choice of Program of Administration Currently we employ programs of more or less continuous administration in most cases although under special circumstances interrupted courses are used But unless these special circumstances dictate it is actually not necessary for the physician to decide definitely at the outset of treatment whether he will use one or the other plan Any preliminary decision can be changed later in the light of the patient s clinical response Thus if interrupted administration is temporarily intended and the patient responds well and tolerates effective maintenance doses but begins to relapse notably during what were to have been the final doses of the initial course of treatment the plan may be converted into one of continuous administration at least for the time being Likewise if the patient embarks on a program of continuous administration but responds well and continues to do so even when the maintenance doses have been

reduced, the physician may decide to continue gradual reduction of dose to the point of discontinuation to see whether or for how long the patient's remission will continue without any hormone

Doses Used for Prolonged Administration Regulation of dosage is a process which requires individualization the dose must be "tailored to fit each patient Hence no set rules can be established at present But in the light of past experience certain generalities can be stated

Initial Doses We have virtually eliminated the use of high initial suppressive doses in our present practice We attempt to start with doses which will be approximately within or only slightly beyond the range estimated as reasonable for prolonged maintenance of the patient taking into account the activity of the disease and the individual's possible susceptibility to side effects We often employ the following daily doses initially for men, 40 to 75 mg for postmenopausal women 20 to 35 mg for other women 30 to 50 mg for children in whom size as well as age must be taken into consideration 15 to 30 mg The smaller doses of each range are given for milder disease the larger doses for more severe Rarely in particularly severe conditions, the limits may be exceeded by a few milligrams

As soon as the antirheumatic response is definite, and even before it is complete gradual dose reduction is initiated—often within a week and occasionally within two or three days if the dose employed produced a marked initial effect or after longer periods if the onset of improvement is slow Sometimes the chosen initial dose may prove to be insufficient in which case one or more small increments, of 5 to 10 mg each may be made but again as soon as a response is obtained reduction of dose should be attempted

Reduction of Dose Decrements vary depending upon such circumstances as the current level of dosage and the response to each reduction in dose Generally decrements are from 5 to 12 5 mg when the daily dose is more than 50 mg from 2 5 to 5 mg when it is 50 mg or less the larger decrements being used also when the response is more marked Likewise the period between reductions varies If the response is marked and the previous reduction well tolerated the dose may be reduced again within two to seven days if the response to the previous reduction has been less favorable another reduction (unless dictated by circumstances other than those relating to the antirheumatic effect) may be delayed as long as necessary for the patient to readjust to the new dose

Maintenance Doses A maintenance dose as said before is not the dose one maintains i e it is not a more or less fixed dose It is that small variable amount required to maintain relief Maintenance refers to relief not dose Just as tolerance for the hormones differs in each patient the proper dose for maintenance of relief varies from patient to patient and from time to time in the same patient hence frequent individual attention is required if the aim of optimal relief without side effects is to be achieved Occasional attempts at reduction should be made even though the patient seems well stabilized on a given dose a lower dose may accomplish as much If the

reduced dose proves insufficient the former dose can be reemployed perhaps for one to three weeks or so before another reduction is attempted

Our past experience suggests that the daily maintenance doses for prolonged treatment generally should not exceed the following limits for men, 65 mg for postmenopausal women 35 mg for other women 45 mg and for children 25 mg In case of increased stress or articular flare temporary use of larger doses may be required

Often no increase in dose is required for mild or moderate flares extra aspirin physical therapy and rest for a few days may suffice If the flare

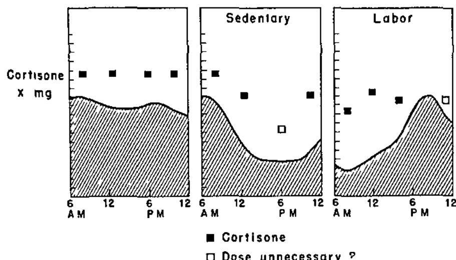


FIG 29 Selective rearrangement of the total daily dose When symptomatic variations are slight during the 24 hours doses should be evenly spaced and evenly divided As the day progresses sedentary patients may improve but laborers may feel worse Fluctuations may be smoothed out by appropriate rearrangements of the timing and divisions of the total daily dose

persists for several days despite these measures the dose may be increased 5 mg for mild or moderate flares 10 mg for more severe flares later a second increment may be given if necessary As soon as the flare begins to recede the dose is reduced again

Rheumatoid symptoms may vary in intensity during each 24 hours (Figure 29) Patients are commonly worse early in the morning better later in the day and perhaps worse again by evening or at some time during the night Where variations are minimal oral doses of cortisone may be divided and spaced more or less evenly But if more marked variations occur the time and amount of individual doses should be adjusted appropriately in order to supply more cortisone during the hours of increased symptoms and to reduce the amount given during the hours when less cortisone is required In this way smaller total daily doses may be successfully employed

Most rheumatoid patients vary symptomatically from day to day (Figure 30) Many have in each week about three average' days two

reduced the physician may decide to continue gradual reduction of dose to the point of discontinuation to see whether or for how long the patient's remission will continue without any hormone

Doses Used for Prolonged Administration Regulation of dosage is a process which requires individualization the dose must be 'tailored to fit each patient Hence no set rules can be established at present But in the light of past experience certain generalities can be stated

Initial Doses We have virtually eliminated the use of high initial suppressive doses in our present practice We attempt to start with doses which will be approximately within or only slightly beyond the range estimated as reasonable for prolonged maintenance of the patient taking into account the activity of the disease and the individual's possible susceptibility to side effects We often employ the following daily doses initially for men 40 to 75 mg for postmenopausal women, 20 to 35 mg for other women, 30 to 50 mg for children in whom size as well as age must be taken into consideration 15 to 30 mg The smaller doses of each range are given for milder disease the larger doses for more severe Rarely in particularly severe conditions these limits may be exceeded by a few milligrams

As soon as the antirheumatic response is definite and even before it is complete gradual dose reduction is initiated—often within a week and occasionally within two or three days if the dose employed produced a marked initial effect or after longer periods if the onset of improvement is slow Sometimes the chosen initial dose may prove to be insufficient, in which case one or more small increments of 5 to 10 mg each may be made, but again as soon as a response is obtained reduction of dose should be attempted

Reduction of Dose Decrements vary depending upon such circumstances as the current level of dosage and the response to each reduction in dose Generally decrements are from 5 to 12 5 mg when the daily dose is more than 50 mg from 2 5 to 5 mg when it is 50 mg or less the larger decrements being used also when the response is more marked Likewise the period between reductions varies If the response is marked and the previous reduction well tolerated the dose may be reduced again within two to seven days if the response to the previous reduction has been less favorable another reduction (unless dictated by circumstances other than those relating to the antirheumatic effect) may be delayed as long as necessary for the patient to readjust to the new dose

Maintenance Doses A maintenance dose as said before is not the dose one maintains i e it is not a more or less fixed dose It is that small variable amount required to maintain relief Maintenance refers to relief not dose Just as tolerance for the hormones differs in each patient the proper dose for maintenance of relief varies from patient to patient and from time to time in the same patient hence frequent individual attention is required if the aim of optimal relief without side effects is to be achieved Occasional attempts at reduction should be made even though the patient seems well stabilized on a given dose a lower dose may accomplish as much If the

reduced dose proves insufficient the former dose can be reemployed perhaps for one to three weeks or so before another reduction is attempted

Our past experience suggests that the daily maintenance doses for prolonged treatment generally should not exceed the following limits for men 65 mg for postmenopausal women 35 mg for other women, 45 mg and for children 25 mg In case of increased stress or articular flare temporary use of larger doses may be required

Often no increase in dose is required for mild or moderate flares extra aspirin, physical therapy and rest for a few days may suffice If the flare

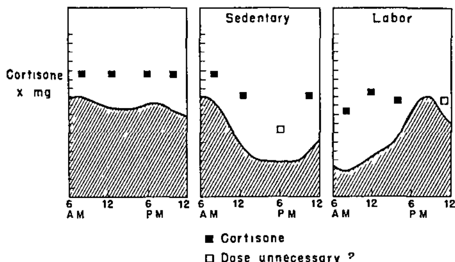


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Most rheumatoid patients vary symptomatically from day to day (Figure 30) Many have in each week about three average days two

"worst" days, and two "best" days Often the patient can tell during the first hours of the day what the rest of the day will be like If such a patient is treated with a fixed dose of cortisone so that he is comfortable all week, he is taking enough for the two worst days more than enough on the other days This mild unrecognized overdosage may make the difference between indefinite tolerance and the slow development of intolerance It would be better for such a patient to regard the lower dose required on the best days as the regular dose to be supplemented as necessary by small increments of

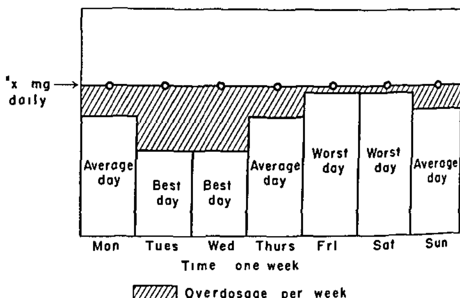


FIG 30 Mild chronic overdosage in a patient with rheumatoid arthritis stabilized on fixed maintenance dose Each week rheumatoid patients commonly have about three average days two worst days and two best days If when receiving a fixed daily dose the patient is equally comfortable all week he is taking enough hormone for his worst days and probably more than enough for the other days of the week Rearrangement and selective variability of doses will correct overdosage

perhaps 2 5 to 5 mg on the other days However such a plan requires an intelligent cooperative patient and careful check of doses to insure that the supplements are not being employed excessively or unnecessarily

Management of Hormonally Treated Patients in Case of Increased Stress

Normally in case of increased stress the body requires and the adrenal cortices under the corticotropic stimulation of the anterior pituitary produce, increased amounts of adrenocortical steroids However treatment with cortisone hydrocortisone or corticotropin temporarily inhibits this normal mechanism during the use of these hormones and for periods varying from days to months afterward Throughout this period of pituitary adrenocortical dysfunction the patient is largely dependent upon exogenously

administered cortisone or corticotropin to supply his need and in case of increased stress sufficient hormone must be given to prevent the serious consequences of adrenocortical insufficiency We recommend that hormone treated patients carry cards similar to cards for diabetic patients and designed to inform those who might care for the patient in an emergency that the patient has been taking these hormones and therefore may need special care [459a]

At present the duration of complete or partial suppression of pituitary adrenocortical function resulting from various doses and periods of treatment with these hormones cannot be predicted accurately Nor are there adequate means of estimating beforehand either the patient's requirement *for adrenocortical hormones under stress or the ability of his pituitary*-adrenocortical mechanism to respond to stress Therefore certain arbitrary precautions seem advisable in the present management of these patients [164 460]

Major Stress Such as Surgical Treatment In the event of surgical treatment of patients who have received cortisone within the preceding six months or within the past two years if hypercortisonism has been present we administer intramuscularly 200 mg of cortisone daily—48 24 and 2 hours before operation 100 mg of cortisone usually is given the day after operation in uncomplicated cases and within the next two or three days the dose is gradually reduced to the preoperative maintenance level Oral administration is resumed about the fifth postoperative day or whenever the *patient is able to utilize medicaments by mouth* [164 460]

For urgent operations in which the preoperative period is insufficient to permit the foregoing prophylactic regimen 200 mg of cortisone should be administered intramuscularly as soon as possible and again immediately before or after operation 100 to 200 mg of cortisone or hydrocortisone in solution should be given intravenously during operation and repeated as needed after operation Treatment thereafter is the same as for patients prepared by the usual prophylactic regimen [9 459]

Adrenocortical insufficiency should be considered a potential hazard in all surgical patients who have had prior therapy with cortisone hydrocortisone or corticotropin Whether or not the foregoing use of extra cortisone is indicated the following precautions are advisable Operation should be performed early in the day to avoid prolonged fasting and other stress incident to waiting If fluids are required intravenously the use of glucose alone *in distilled water should be avoided physiologic sodium chloride solu*tion or 5 per cent glucose in physiologic sodium chloride solution should be given instead Morphine which is poorly tolerated by patients who have adrenocortical insufficiency should not be used particularly if prophylactic treatment with cortisone has not been given meperidine hydrochloride (Demerol) may be substituted

During and after operation the patient is observed closely blood pressure pulse and temperature are checked hourly for 24 to 36 hours If signs of adrenocortical insufficiency (weakness tachycardia hypotension vascular collapse respiratory failure fever) develop 100 mg of cortisone or hydro

cortisone in solution* is promptly administered intravenously and is repeated along with additional saline solution as often as necessary to maintain normal blood pressure 200 mg of cortisone is given intramuscularly for its delayed effect Aqueous adrenocortical extract in sodium chloride solution may be used for patients in critical condition or in the event that cortisone or hydrocortisone for intravenous use is not immediately available An intramuscular injection of 40 cc of the adrenocortical extract may be given in each of two sites 40 cc of the same extract in a liter of saline solution may be administered intravenously in four hours this latter being repeated every four hours for as often as is necessary Also oxygen blood transfusions and vasopressor drugs such as norepinephrine 4 mg added to sodium chloride solution are used as indicated for patients in shock Appropriate modifications of these prophylactic and therapeutic regimens can be applied to instances of severe stress other than surgical procedures e g, severe infection or severe trauma

Minor Stress For minor stress such as slight upper respiratory infection mild influenza or slight trauma the maintenance dose may be continued or increased slightly by 10 to 25 mg daily Careful clinical observation should reveal any need for additional amounts of hormones

Results

Our own results from the long term use of cortisone can be summarized thus The arthritis of 50 per cent or more of our patients has been controlled rather easily by apparently safe and relatively low maintenance doses Dose adjustments were occasionally necessitated by spontaneous flares trauma or intercurrent infections About 35 per cent of our patients have required closer attention and frequent changes in doses In some patients increased doses temporarily required may induce side effects for which supplemental measures are needed transiently These patients have been more difficult to handle than the first group but results are often satisfactory In about 15 per cent of our patients the continuous adequate control of the disease with tolerable doses has been difficult if not impossible with present schemes of hormonal treatment because of the severity of the disease or other poorly understood factors

Common Reasons for Unsatisfactory Results from Use of These Hormones

Certain correctable mistakes have been responsible for some of the unsatisfactory results obtained by us or others The most common of these have been (1) improper selection of patients for treatment rheumatoid patients with complicating conditions which contraindicate the use of hormones or those with irreversible changes and little or no active inflamma

* The suspension of cortisone acetate and hydrocortisone acetate should not be administered intravenously cortisone or hydrocortisone for intravenous use should be in solution

tion, or other patients who do not have diseases responsive to hormonal therapy (2) inadequate supervision of patients insufficient clinical observation and failure to recognize early signs of hypercortisonism (3) improper regulation of dosage administration of excessive doses or less commonly insufficient doses too abrupt reduction or withdrawal of dosage improper division and spacing of the total daily dose erratic dosage (rapid vacillation from overdosage to underdosage to overdosage) failure to regulate dosage in accordance with patient s need and tolerance for cortisone e g failure to reduce dose when signs of hypercortisonism appear or to increase dose temporarily for bona fide rheumatoid flares (4) neglect of supplemental measures of treatment (5) insufficient rest and excessive trauma to joints (6) failure to use supplemental doses of hormones during increased stress [164 460] The results of therapy can be improved considerably if mistakes such as these are avoided

Hormonal Treatment of Certain Other Rheumatic or Articular Diseases

Cortisone hydrocortisone and corticotropin have been employed in treatment of other rheumatic or articular diseases some of which will be mentioned briefly In many of the noninfectious self limited diseases hormonal treatment has been employed most successfully In chronic indefinitely prolonged disease the possibilities of benefit from use of the hormones are limited to a certain extent as in rheumatoid arthritis by the necessity for compromise in regulating the dosage in order to avoid side effects

Arthritis of Allergic Reactions Corti one and corticotropin effectively control the arthritis of allergic reactions such as serum sickness or drug reactions [9 461] They are u eful in the treatment of severe or moderately severe allergic reactions which are not adequately controlled by such measures as the use of antihistaminic agents salicylates and local application of heat Doses of 75 to 100 mg or occasionally more of corti one or 30 to 40 units or more of corticotropin depending upon circumstances may be given daily for a few days until the manifestations of the reaction subside then the dose may be tapered and treatment finally discontinued after these elf limited conditions have run their usual course of one to three weeks rarely longer

Arthritis of Chronic Ulcerative Colitis The articular reactions associated with chronic ulcerative colitis can be suppressed by hormonal therapy However treatment of the colitis usually is of primary importance in these cases and the role of cortisone in that regard is in di pute among gastroenterologists If hormonal therapy is indicated and employed for the arthritis dosage should be regulated as advised for treatment of rheumatoid arthritis

Bursitis, Epicondylitis, Periarthritis, Shoulder-Hand Syndrome, Tendinitis, Tenosynovitis Favorable results[100 139 13 431 46 –464] have been reported from the u e of cortisone or corticotropin for noninfectious forms of the e conditions Such treatment generally has been more successful if

employed in the acute rather than the chronic stage of the disease However, hormonal treatment has been helpful when used in conjunction with orthopedic manipulation of frozen shoulder Local injection of hydrocortisone acetate is superior to systemic administration in some cases in which the process is well localized to a site that is easy to inject [245]

Fibrositis The symptoms of fibrositis respond favorably to hormonal treatment but because of the possible complications of prolonged therapy the use of these hormones is not considered advisable in most cases [59]

Gouty Arthritis Cortisone and corticotropin suppress the clinical manifestations of attacks of acute gouty arthritis [22 74 101 106 207 213 3 431 44 465–470] Yet paradoxically an attack of acute gouty arthritis may be precipitated when administration of these hormones is discontinued such a rebound attack can be prevented by administration of colchicine with and subsequent to use of the hormone Hence colchicine is still regarded as the drug of choice in acute gouty arthritis For the rare colchicine-resistant attack cortisone (100 mg by mouth every eight hours) or corticotropin (50 units of the aqueous solution given intramuscularly every six hours) may be administered until the acute attack is controlled then use of the hormone may be discontinued and colchicine (0 6 mg two to three times daily) should be administered orally for about three to seven days

These hormones also promote the renal excretion of uric acid but other uricosuric agents such as salicylates or Benemid are preferable since they accomplish the same purpose without the risks of prolonged hormonal therapy

Hemophilic Arthritis The administration of cortisone to a patient who had degenerative joint disease secondary to hemophilia was reported as of no value [3]

Lupus Erythematosus The use of these hormones in the treatment of lupus erythematosus is discussed in detail in Chapter 5 Suffice it to say here that the articular reaction can be suppressed by hormone administration

Osteoarthritis The systemic use of cortisone or corticotropin in osteoarthritis has resulted in little if any improvement according to most investigators although in a few cases [66 99 101 218 23 430 431 471 47] some temporary relief has been reported In view of the possible complications of treatment and the relative lack of favorable results it is generally agreed that the systemic use of these hormones is not indicated in this disease On the other hand the intra articular injection of hydrocortisone acetate for its local antirheumatic effect has been a useful adjunct to but not a replacement for standard measures of treatment particularly for acute or subacute exacerbations in the large weight bearing joints [45 50]

Palindromic Arthritis The value of hormonal therapy in palindromic arthritis has not been well defined to date More experience will be necessary in order to evaluate the possible benefits of maintenance therapy as compared to those from intermittent therapy given only at the time of individual attacks

Psoriatic Arthritis The treatment of psoriatic arthritis with cortisone or corticotropin is generally comparable to that of rheumatoid arthritis [10, 138, 464, 473–476] although slightly less favorable results have been noted by some [212] Addition of general measures and appropriate dermatologic treatment are important in achieving the best results

Reiter's Syndrome The manifestations of Reiter's syndrome generally respond favorably to the administration of cortisone or corticotropin Dosage should be regulated and other general measures of treatment should be carried out much as for rheumatoid patients [53, 8, 464, 477, 4, 8]

Specific Infectious, or Septic, Arthritis Systemic hormonal treatment is not indicated for specific infectious arthritides such as those caused by pyogenic organisms or tuberculosis

Acute Traumatic Arthritis Hormonal therapy in conjunction with other standard measures may be of considerable supplementary value in acute traumatic arthritis [463] However the intra articular injection of hydrocortisone acetate appears to be more efficient than systemic administration for this purpose [245]

Conclusions

Cortisone hydrocortisone and corticotropin by virtue of their anti rheumatic and anti inflammatory activity have stimulated great interest in rheumatic and many other diseases not only in the fields of basic scientific and clinical investigation but also in the field of clinical therapeutics

The final role of these hormones in clinical medicine must await further experience As now employed hormonal therapy is more satisfactory in responsive acute self limiting diseases than in chronic diseases But it is valuable even now in many cases of rheumatoid arthritis and often is the treatment or supplement of choice

Above all else these hormones constitute the most useful research tool ever developed for the study of rheumatic and certain other diseases They still belong as much if not more to physiologists and clinical investigators as to rheumatologists and other physicians Continued progress will certainly be made—some of it by evolution some by revolution in science From the many physiologic biochemical and clinical studies under way will come a great increase in our knowledge of these hormones and of the pathogenesis and control of the diseases which they influence

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4

Rheumatic Fever

Joseph J Bunim

Observations on the effects of cortisone upon rheumatic fever and evaluation of its therapeutic usefulness, as presented in this chapter are based largely on a study of 44 patients conducted at the New York University Bellevue Medical Center in extension of a previous report [1] Five years ago Hench and his associates[2] at the Mayo Clinic published the first report on the spectacular effects of cortisone and corticotropin in rheumatic fever Reports by others since then include in the aggregate observations on more than 150 well documented cases In January 1951 the Council on Rheumatic Fever of the American Heart Association in collaboration with the British Medical Research Council initiated a carefully designed study on the relative value of cortisone corticotropin and salicylates in the treatment of rheumatic fever and the prevention of rheumatic heart disease at 13 research centers in the United States Great Britain and Canada Approximately 660 cases have been observed in the first 18 months and a forthcoming analysis of the collected data is anticipated References to a preliminary report of this international study and to the other papers mentioned will be made where data from our cases are inadequate and especially where our findings (Table 20) and conclusions are at variance with those reported by others

In rheumatic fever as in other diseases it is important to distinguish direct suppression of clinical and laboratory signs induced by cortisone or corticotropin from their effect upon intrinsic pathologic processes and to determine whether these hormones have the capacity to alter or arrest the course of the disease to reverse any structural changes or to prevent tissue damage To help draw such a distinction and estimate the real value of hormonal therapy in rheumatic fever one should divide the diverse manifestations of the disease into two categories In the first group should be included the nonspecific clinical and laboratory signs which accompany other infec

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Table 20

RESULTS OF HORMONAL THERAPY IN 44 PATIENTS WITH RHEUMATIC FEVER

	Number of Attacks	
	Initial	*Recurrent*
Total Number of Patients Treated	30	14
A *Without Carditis before Therapy*	13	3
Recovered without organic heart disease	13	2*
C-Reactive Protein		
Present before therapy	13	3
Disappeared during therapy	13	3
Erythrocyte Sedimentation Rate		
Elevated before therapy	13	3
Reduced to normal during therapy	12	2
B *With Carditis before Therapy*†	17	11
Recovered without organic heart disease	2	2
Active carditis present after therapy	6	7
Congestive Failure		
Present before therapy	7	1
Disappeared during therapy‡	7	0
Pericarditis		
Present before therapy	5	0
Disappeared during therapy‡	5	0
Enlarged Heart		
Present before therapy	15	10
Reduced to normal during therapy‡	2	1
Mitral Systolic Murmur (organic)		
Present before therapy	17	11
Disappeared during therapy*	2	2
Mitral Diastolic Murmur		
Present before therapy	13	8
Disappeared during therapy*	5	2
Aortic Diastolic Murmur		
Present before therapy	6	2
Disappeared after therapy*	1	0
Gallop Rhythm		
Present before therapy	13	5
Disappeared during therapy	11	5
Tachycardia (out of proportion to temperature)		
Present before therapy	15	8
Disappeared during therapy‡	6	2
C-Reactive Protein		
Present before therapy	17	9§
Disappeared during therapy	17	7‖
Erythrocyte Sedimentation Rate		
Elevated before therapy	17	11
Reduced to normal during therapy	14	6
C *With Subcutaneous Nodules*		
Present before therapy	5	0
Disappeared during therapy*	5	0
Appeared during therapy	0	0

* One patient had antecedent heart disease

† One patient who had two separate attacks (described in the text and in Figure 32) is considered here as two cases

‡ No recurrence after therapy

§ C-reactive protein not done on 2 patients

‖ Two patients received inadequate therapy

tious diseases, such as increase in temperature and heart rate, "toxicity," loss of appetite anemia, accelerated erythrocyte sedimentation rate increased concentration of plasma fibrinogen and serum globulin, and the appearance of C reactive protein in the blood The second category consists of the signs more specifically characteristic of rheumatic fever These may again be subdivided into "extracardiac" features i e polyarthritis, subcutaneous nodules chorea and erythema marginatum, and signs which indicate inflammation or proliferation of the structures of the heart i e pericarditis myocarditis and endocarditis or valvulitis

Although several of the questions particularly the basic ones remain yet to be resolved most of them have been answered albeit without unanimity in some instances In general observers agree that the favorable effects of cortisone on all the nonspecific and certain specific rheumatic manifestations, both cardiac and extracardiac, are pronounced, uniform and quite prompt, on other rheumatic manifestations the hormonal influence is equivocal and on some the steroid exerts no effect (Table 21)

Table 21

EFFECTS OF CORTISONE UPON ACTIVE RHEUMATIC FEVER AND CARDITI

Nonspecific	*Antirheumatic*	
	Positive	*Questionable or Negative*
Temperature falls Heart rate decreases Toxicity disappears Well being develops Appetite increases Hemoglobin rises Return toward or to normal of L S R Fibrinogen Gamma globulin C reactive protein	Polyarthritis subsides promptly Pericarditis subsides (spontaneous or the result of therapy?) Congestive heart failure improves (salt free diet) Quality of heart ounds improves Gallop rhythm usually disappears	Subcutaneous nodules—disappearance probably accelerated Effect on chorea doubtful Erythema marginatum unaffected Endocarditis unaffected? Murmurs suggesting organic heart disease usually persist even in patients treated early in first attack In the absence of pericardial effusion heart size unaffected In myocarditis tachycardia often persists even if the temperature is controlled Chronic myocarditis unaffected

Effect of Cortisone upon Nonspecific Signs

Fever and Tachycardia Almost without exception the temperature is reduced to normal within three days following oral administration of adequate amounts of cortisone The higher the temperature the more striking is the effect of the hormone The fall in the resting pulse rate usually parallels

the drop in temperature unless severe carditis is present in which case increased doses of cortisone will usually result in a gradual reduction of the heart rate It seems likely then, that to a large extent the fall in pulse rate observed when cortisone is given in average doses may be secondary to defervescence rather than a result of a direct effect of the hormone upon myocardial function, inflammation or the vagal activity When cortisone is given intramuscularly, the response is delayed somewhat because of slower

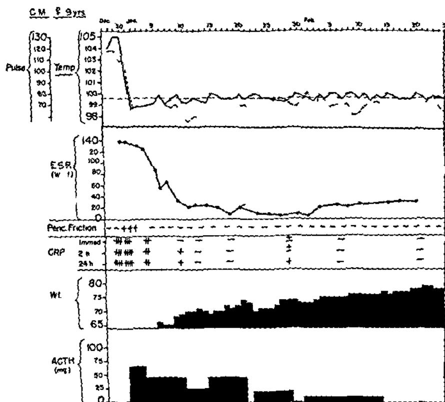


Fig 31 Response of a patient with rheumatic fever polyarthritis and carditis to treatment with corticotropin instituted on eighth day of initial attack E S R = Erythrocyte Sedimentation Rate Peric Friction = Pericardial Friction Rub CRP = C Reactive Protein Wt = Weight in pounds (Slightly modified from Bunim [22]) *Note* In this and subsequent figures ACTH refers to corticotropin

absorption The response to corticotropin is essentially more rapid than that to cortisone but otherwise the same (Figure 31)

'Toxicity' and Well-Being Probably the most dramatic effect of hormonal therapy is upon the 'toxic' state of the patient Children severely ill with rheumatic fever are usually weak prostrated apathetic withdrawn tachypneic febrile flushed or strikingly pale anorexic occasionally restless and in extreme cases delirious On the second or third day of cortisone therapy remarkable improvement occurs All of these symptoms are gone

the patient appears cheerful and is again interested in his food, toys and environment

Erythrocyte Sedimentation Rate The erythrocyte sedimentation rate (E S R) is almost invariably elevated in rheumatic fever except in some cases in which it is complicated by congestive failure Of the various constituents of plasma fibrinogen is believed to be the most important single factor causing an accelerated E S R Administration of cortisone is followed in nearly all cases by a depression in the E S R , and in a decided majority by a return to normal rate in the second or third week of therapy A fall in the plasma fibrinogen concentration parallels the drop in E S R This has been observed however in diseases other than rheumatic fever Furthermore it has been demonstrated that a single injection of corticotropin in normal persons will result in a significant reduction of plasma fibrinogen [3] These observations suggest that adrenocortical therapy may have a direct and nonspecific effect upon the E S R An E S R suppressed to normal limits in a rheumatic fever patient receiving cortisone should not be interpreted as indicating a cessation of rheumatic activity

C-Reactive Protein A more sensitive index of rheumatic activity than the E S R is a precipitin test which detects the presence of a protein not occurring in normal serum but appearing in the blood during rheumatic fever and disappearing when the inflammatory process becomes inactive [4] This test is not specific for rheumatic fever and has been found positive in a number of unrelated diseases [5]

Sera of all but 2 patients in our series have been analyzed for C reactive protein (C R P) at frequent intervals before during and after hormonal therapy * In all cases the test was strongly positive before treatment, and in all except 2 patients inadequately treated it became negative within a week or two after therapy was begun usually before the E S R reached normal When however hormonal administration was discontinued the C R P temporarily reappeared in 40 per cent of the cases, and when rheumatic activity continued the positive reaction persisted [6] Since this effect of the hormone upon the C R P is consistently seen both in cases in which the rheumatic process has become inactive and in those in which activity is merely suppressed it seems clear that the absence of C R P from the serum of a patient receiving cortisone should not be interpreted as evidence of subsidence of activity The disappearance of C R P may result from direct action of the hormone on protein metabolism

Antihyaluronidase and Mucoproteins Adams and his associates[7] reported that administration of corticotropin to patients with rheumatic fever was followed by a rapid fall of the nonspecific hyaluronidase inhibitor from abnormally elevated pretreatment levels to subnormal values within 10 to 15 days, whereas the serum mucoproteins which are also increased in rheumatic fever returned to normal levels much more slowly in three to four

* We are indebted to Dr Harrison Wood of The Rockefeller Institute for Medical Research New York for generously furnishing us with serum for testing the presence of C R P

months These workers found that when corticotropin was discontinued or the dosage excessively reduced before a substantial drop in the mucoprotein level had occurred the patient had a recurrence of the disease

Gamma Globulin This protein constituent of the serum is usually increased in patients with rheumatic fever and is reduced to normal values shortly after cortisone therapy is begun Changes in the serum globulin concentration did not parallel the E S R as consistently as did the plasma fibrinogen

Relation of Severity and Duration of Illness to the Response to Cortisone

There frequently is not a good correlation between the degree of abnormal deviation of the nonspecific signs just enumerated and the severity of the disease Indeed it is noteworthy that the E S R as measured by Wintrobe s method (uncorrected) in the vast majority of our patients fell within the narrow limits of 50 to 60 mm per hour regardless of whether a patient had severe moderate or slight carditis (provided of cour e that congestive failure had not supervened) or no carditis at all Similarly the test for C R P on the serum of most patients was positive to the same degree (3+ to 4+)

With adequate doses irrespective of the severity of the disease or the length of the interval from onset to the beginning of treatment abnormal nonspecific signs return toward or to normal Although tachycardia associated with fever is easily controlled tachycardia due to myocarditis usually does not respond unless massive doses are used With such large amounts of hormone undesired effects often develop As soon as the dosage is reduced even slightly tachycardia usually recurs

Effect of Cortisone upon Signs Characteristic of Rheumatic Fever

Polyarthritis Within three to four days of oral administration of cortisone all signs and symptoms of joint inflammation are gone regardless of severity extent or duration of the arthritis When cortisone is given intramuscularly this response may be delayed for one or two days because of slower absorption Extension of acute inflammation to previously unaffected joints during adequate cortisone therapy is rare it has not occurred in our series

Subcutaneous Nodules It is difficult to evaluate the effect of cortisone upon these subcutaneous lesions of rheumatic fever which almost always are associated with carditis They usually become smaller and disappear during cortisone therapy although they may occasionally increase in number despite treatment very rarely if ever do they appear for the first time after hormone administration has been instituted The rate of disappearance of the nodules varies from a few days to seven weeks Since nodules often disappear spontaneously within this period it is difficult to measure the influence of hormonal therapy on the dissolution of rheumatic subcutaneous granulomas

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In treating patients with rheumatic carditis it is necessary therefore to restrict sodium chloride intake to 1.0 Gm or less daily. It is important to observe these patients very carefully and in the more severe cases it may become necessary to administer oxygen, mercurial diuretics or digitalis.

Eight patients in our series presented signs of congestive failure on admission. In 5 the failure cleared during hormonal therapy without the aid of digitalis or diuretics. Of the 3 who required either or both of these adjuvants, 1 child did not adhere to a salt poor diet. To only 1 patient adequately treated with adrenocortical hormone and maintained on a salt poor diet was it necessary to administer digitalis and Mercuhydrin to combat failure. This patient was 2½ years old and was admitted to the hospital in a critical condition two weeks after the onset of an initial attack of rheumatic fever with severe carditis. For this and another seriously ill patient in the group with congestive failure it is our impression that hormonal therapy was a lifesaving measure.

Dorfman and his associates[9] reported the presence of congestive failure prior to hormonal therapy in 13 patients. In 3 failure was intensified during treatment but was controlled by mercurial diuretics or withdrawal of corticotropin for short periods. In 10 patients evidence of failure disappeared during therapy and did not recur after the drug was discontinued. Similar results were reported in 6 cases by Massell and Warren.[8]

Size of Heart. It is doubtful that the hormones directly affect the size of the heart during acute carditis. In the absence of pericardial effusion, a decrease in the size of the heart was rarely observed in our cases during or soon after cortisone therapy, even when the enlargement was recent and signs of activity were suppressed. Other observers[9] have reported a decrease in cardiac size of at least 25 per cent in half their cases.

Electrocardiographic Changes. Delayed conduction of impulses from the right atrium to both ventricles, as reflected in prolongation of the P-R interval, is usually abolished within the first week of hormonal therapy. This may often occur, however, with bed rest and conventional therapy. That cortisone may be active in suppressing delay in impulse conduction is suggested by the reappearance in some cases of P-R interval prolongation when the hormone is withdrawn. Conduction defects may develop for the first time during or after hormonal therapy. Prolongation of the P-R interval resulting from antecedent heart disease is not altered despite marked clinical improvement.[13] Other electrocardiographic abnormalities, such as T wave and S-T segment changes, are inconsistently affected by hormonal therapy.

Heart Rate. With a fall in temperature induced by cortisone there is a concomitant and proportional reduction in the cardiac rate in patients with rheumatic fever who do not have active carditis. In the absence of fever tachycardia resulting from carditis does not readily respond to the usual doses of cortisone. Increasing the dose two- or threefold may reduce the rate. In 15 of 22 cases of carditis associated with tachycardia out of proportion to temperature, the rapid and labile rate persisted despite adequate hormonal therapy.

Chorea The duration of untreated chorea a self limited disease is variable and its spontaneous termination unpredictable Under such circumstances it is difficult to assess the therapeutic value of any agent especially in a small number of patients Furthermore the effect of cortisone upon chorea is rarely striking often equivocal and inconsistent There are therefore no clearly affirmative indications for the employment of cortisone in cases of pure chorea that is not associated with other rheumatic manifestations

Erythema Marginatum This evanescent cutaneous lesion though characteristic of rheumatic fever is symptomless and requires no special attention Cortisone has no definite effect upon erythema marginatum The eruption not infrequently appears or recurs during hormone administration

Pericarditis The clinical signs of pericarditis (pericardial friction rub with or without pericardial effusion) disappeared within 14 days of hormonal therapy in every one of the 6 cases reported by Massell and Warren [8] in 7 cases observed by Dorfman and his associates [9] and in 10 cases included in our series These 23 cases consisted of initial and recurrent attacks of short and long duration prior to therapy In one of our patients typical electrocardiographic changes associated with pericarditis did not completely disappear until the thirtieth day of therapy although the friction rub was no longer audible by the seventh day In none of our patients in this series did a friction rub first appear or reappear during treatment Although the effect of hormonal therapy upon pericarditis is uniform and impressive it should be recalled that acute pericarditis in rheumatic fever usually disappears even without specific antirheumatic treatment

Congestive Heart Failure Congestive failure due to acute rheumatic carditis often responds to adequate doses of cortisone Hormonal therapy is particularly valuable in such cases provided salt intake is restricted

It is well known that cortisone and corticotropin induce water and sodium retention Ziff Simson and Bunim[10] have demonstrated that administration of corticotropin to patients with or without heart disease on unrestricted salt intake is followed by a consistent increase in total body water In some patients this increase causes expansion of the extracellular compartment in other patients there is retention of fluid in the intracellular space with gain in tissue weight and in some both extra and intracellular space are augmented Levitt and Bader[11] reported a consistent shift of water (up to 4 500 ml) from the intracellular to the extracellular compartment reaching a maximum after eight to nine days of administration of cortisone or corticotropin (in the absence of an over all positive sodium chloride or water balance and without an increase in body weight) in a group of patients with rheumatic diseases maintained on a salt free diet Albert Smith and Eichna[1] found that when the hormones are given to patients who have normal cardiac function without organic heart disease and are permitted unrestricted diets the circulation may become congested as indicated by an increase in venous right atrial right ventricular and pulmonary arterial pressures and by an augmented circulating blood volume

sented no signs of residual cardiac damage at the end of treatment or during the following year of observation Of these 3 1 patient was observed in an initial attack and 2 in recurrent attacks In other words among a total of 28 patients (17 experiencing initial and 11 recurrent attacks 10 treated within the first two weeks of illness and 18 treated later) with unequivocal signs of active rheumatic carditis prior to hormonal therapy only 4 (2 in initial and 2 in recurrent attacks) recovered completely without stigmata of cardiac disease In 2 additional patients experiencing initial attacks diastolic apical murmurs disappeared during hormonal therapy but apical systolic and aortic diastolic murmurs persisted and the heart remained enlarged Nine of 11 patients in whom murmurs persisted during recurrent attacks had not been examined by us prior to onset of the recrudescence Whatever organic murmurs might have resulted from previous attacks could not be expected to disappear as a result of hormonal therapy There is no question but that preexisting valvular deformities and cardiac hypertrophy are irreversible

At any rate the e results are not superior to those observed by Bland and Jones[14] prior to the advent of cortisone or corticotropin It should be noted however that in none of the patients with carditis was there evidence of extension of structural damage during hormonal therapy

At variance with some of these conclusions is a report by Wilson and Helper [15] Eleven con ecutive patients 6 to 18 years of age with early acute rheumatic carditis were treated with daily doses of 30 to 100 units of cortico tropin for only seven days Three patients received a second course similar to the first The authors report that in every patient clinical evidence was obtained of termination of symptoms and signs of progressive acute carditis during therapy Four to 12 months after treatment of the 6 patients with an initial attack there was no evidence of residual cardiac damage in 2 and equivocal evidence in 3 So far no other observer has reported similar re ults

Although organic murmurs do not commonly disappear and cardiac damage is seldom prevented even when hormonal therapy is instituted early in the course of acute rheumatic carditis it is the impression of several independent observers[3 16 17] that more favorable re ults are achieved when treatment is begun early within a few days after onset This is illustrated by a case from our series

Case Report

A boy of 4 years was ob erved in two separate attacks of active rheumatic carditis In the first attack treatment was begun during the fifth week of illness in the second bout it was started on the second day The clinical course and response to therapy are charted in Figure 32 This boy was first admitted on the thirty first day of his initial attack complaining of fever and leg pains There was no history of sore throat polyarthritis or chorea When admitted he was acutely and seriously ill and exhibited signs of congestive failure He was orthopneic and dyspneic and his liver was enlarged to 6 cm below the costal margin The heart sounds were overactive and of poor quality A gallop rhythm was present and the rate was 120 per minute The temperature was 101 F Grade 2 systolic and diastolic murmurs were heard at the

Gallop Rhythm Gallop rhythm is considered by many observers to be suggestive of active rheumatic carditis This sign disappears in most cases within the first week or two of cortisone therapy It rarely occurs for the first time during hormonal treatment

Murmurs and Residual Cardiac Damage Considerable attention has always been focused on new and changing murmurs during the course of rheumatic fever because they are universally accepted as auscultatory evidence of active carditis The significance of a murmur increases with its intensity extent of transmission and constancy

Significant murmurs even of recent origin do not usually disappear as a result of hormonal therapy In our series 10 patients who had active carditis have been treated with cortisone or corticotropin or both in 3 to 14 days from the onset of initial or recurrent attacks (Table 22) Six of these 10 were treated during initial attacks and in only 1 of the 6 did all murmurs disappear Periodic reexamination of this patient for 15 months after treatment revealed no signs of organic heart disease In the other 5 none of the murmurs present prior to treatment disappeared Once therapy was instituted however no new murmurs developed during either an initial or recurrent attack

Table 22

RESULTS IN PATIENTS TREATED WITHIN 14 DAYS AFTER ONSET

Case	Age (Years)	Attack	Day from Onset to Treatment	Severity of Carditis	Hormone Used	Days Given	Follow-up Period (Months)	Residual Heart Disease
1	6	First	4	Mild	Corticotropin	4	11	Mitral insufficiency
	10	First	4	Severe	Cortisone	4	15	No[illegible]
3	8	First	8	Moderate	Corticotropin	46	19	Enlarged heart Mitral insufficiency
4	4	First	9	Severe	Corticotropin Cortisone	3 34	14	Enlarged heart Mitral insufficiency
5	5	First	14	Moderate	Cortisone	1	14	Mitral insufficiency
6	2	First	14	Severe	Corticotropin Cortisone	4 4	14	Enlarged heart Mitral insufficiency
7	12	Fifth	3	Mild	Cortisone	4	9	[illegible] Mitral insufficiency and [illegible]
8	1	Third	6	Mild	Cortisone	44	1	No change [illegible]
9	9	Second	9	Severe	Corticotropin	9	0	No change Mitral insufficiency
10	20	Second	13	Severe	Corticotropin Cortisone	18 8	3	No change Mitral insufficiency [illegible]

Three patients among 18 with active rheumatic carditis who were treated later than 14 days from the onset (27 29 and 39 days respectively) pre

dosage schedule established for the first course was much more rapid and favorable Congestive heart failure did not develop the aortic diastolic murmur did not appear and gallop rhythm was absent It will be noted in Figure 32 that the apical diastolic murmur (which disappeared between the two attacks and returned at the onset of the second) and the tachycardia did not persist as in the first episode The test for C R P became negative on the twelfth day of treatment

Further evidence that favorable results may be achieved when cortisone is administered early in the course of rheumatic carditis has recently been advanced by Greenman and associates [13] Forty eight children 4 to 15 years of age in initial attacks of rheumatic carditis were treated with higher than conventional doses of cortisone as long as activity persisted The majority received the steroid orally for eight weeks in doses of 300 mg daily for six weeks and in decreasing amounts for another two weeks Sodium intake was restricted to 50 mg daily Of 12 children with carditis (5 had heart failure) treated within two weeks of onset 10 recovered without residual cardiac damage Of 23 children with carditis (8 had heart failure) treated between two and six weeks after onset 16 escaped residual organic heart disease However of 13 children with carditis treated after six weeks of onset only 1 had a normal heart after treatment was completed

Undesired Effects

Few children who receive cortisone or corticotropin for several successive weeks escape the temporary undesired effects of these hormones (Table 23) It is remarkable however that so few patients with active carditis develop superimposed congestive failure due to the water and salt retention and adverse hemodynamic changes which often follow adrenocortical therapy To avoid this complication it is necessary as mentioned to restrict salt intake

Table 23

INCIDENCE OF TEMPORARY UNDESIRED EFFECTS IN 44 PATIENTS WITH RHEUMATIC FEVER (AGES 2 TO 20 YEARS) DURING HORMONAL THERAPY

Effect	Number
Moonface	38
Abnormal fat deposits	23
Acneform eruption	14
Hirsutism	12
Striae	8
Peripheral edema	7
Liver enlargement (without congestive failure)	6
Abdominal distention	6*
Pigmentation	6
Tremors	4
Furunculosis	4
Glycosuria (trace)	3
Insomnia	2
Hypopotassemia	2
Petechiae	1

* All patients were under the age of 8 years

Enlargement of the liver not secondary to congestive failure is seen with greater frequency in children receiving hormonal therapy than in adults In

apex and a grade 1 diastolic murmur at the aortic area. The congestive failure cleared after six days of therapy. Gallop rhythm persisted but the aortic diastolic murmur was not heard after the third week of treatment. The apical mid-diastolic murmur was heard throughout the six week period of hormone administration although its intensity diminished after a few weeks. The tachycardia persisted and the pulse remained labile. The C R P disappeared slowly.

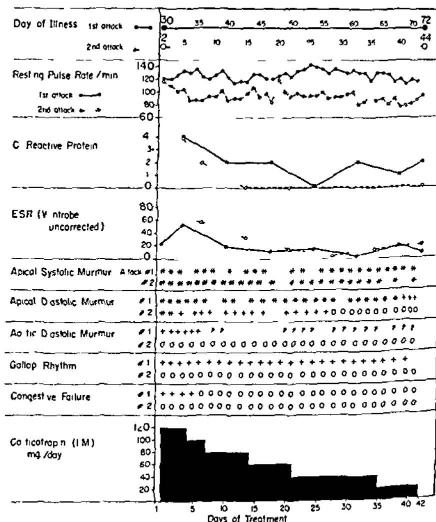


Fig 32 Results of early and late treatment in a patient seen during two attacks of active rheumatic carditis

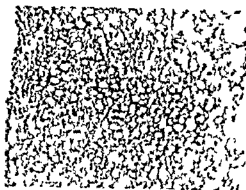
Six months after corticotropin was discontinued the patient returned to his own home from a convalescent home. At his home he neglected to take sulfadiazine for three successive days. One sibling had had pharyngitis when the patient returned. On April 3 the patient developed an acute pharyngitis. On April 4 a throat culture was taken and penicillin was injected intramuscularly. The following day hemolytic streptococci were found in the throat culture. From April 4 to April 17 the patient received 2 400 000 units of penicillin intramuscularly. Despite the chemotherapy on April 17 recrudescence of acute rheumatic carditis developed. On April 19 corticotropin therapy was begun. The response to this course given according to the



Fig 34 Abdominal distention and adiposity resulting from cortisone administration *This child of 2 years received an aggregate of 6.0 Gm of cortisone for severe* acute rheumatic carditis The abdominal contour returned to normal several weeks after hormonal therapy was discontinued (From Bunim [22])

occurred rapidly (one week) in some and very slowly (several months) in others Biopsy of the liver performed in 2 of these patients *during the maximum* degree of hepatomegaly revealed marked fatty infiltration In one case a second biopsy done 20 days later following cessation of cortisone disclosed a striking diminution in the amount of fat deposited [9] (Figure 33)

a combined group of patients observed at Irvington House, Lenox Hill and Bellevue Hospitals. Baldwin and Rusoff[19] noted hepatomegaly in 15 of 39 children 5 to 14 years of age who were treated for rheumatic fever with cortisone or corticotropin for an average of six weeks. Although there had been evidences of active carditis early in the course of 5 of the 15 cases these

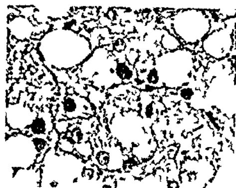




Low Power

Liver biopsy taken 7 days following completion of 6 week course of cortisone therapy showing marked fatty infiltration

Liver biopsy taken 27 days following completion of cortisone therapy showing marked regression of fatty infiltration





High Power

7 days post ℞

27 days post ℞

Fig 33 Biopsy of the liver of a boy of 14 with recurrent carditis and rheumatic heart disease. An aggregate of 3 075 Gm of cortisone was administered over a period of 43 days. Congestive failure was absent. The liver was not palpable prior to therapy but became palpable on the sixth day of cortisone. On the day of first biopsy (7 days after cortisone was discontinued) the liver edge was at the level of the umbilicus. On the day of second biopsy (27 days after cortisone was stopped) the liver was no longer palpable. (From Steinberg, Webb and Rafsky [20])

signs had disappeared before the maximum degree of hepatomegaly was attained. In none were there symptoms or signs of congestive failure. The liver border extended as much as 4 to 6 cm below the costal margin in two-thirds of the cases. Maximum size was usually reached by the end of the second or third week of treatment. The organ was smooth and not tender. Regression of the liver to normal size on termination of hormonal therapy

ena is not apparently related to the interval from onset to therapy duration of treatment severity of illness or the number of antecedent attacks of rheumatic fever Occasionally the intensity of the rebound is greater than the initial manifestation *Without reinstitution of therapy the rebound subsides* In fact a rebound is distinguished from a recurrence or persistence of rheumatic activity by its spontaneous disappearance within a relatively short period *Since a rebound does not require re treatment its recognition is of*

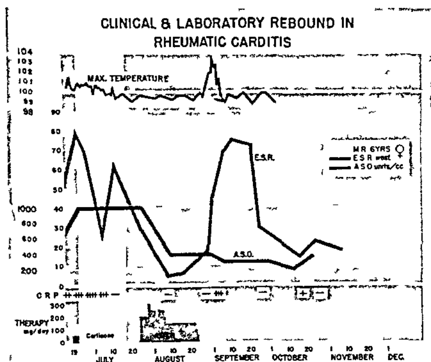


Fig 35 Response of the temperature erythrocyte sedimentation rate (E S R) antistreptolysin O titer (A S O) and C reactive protein (C R P) to administration of cortisone and corticotropin and to their withdrawal

practical importance Figure 35 graphically illustrates a case of clinical and laboratory rebound which is described in the following report

Case Report

To a 6-year-old child admitted in the fifteenth week of her first attack of rheumatic fever with severe carditis hormonal therapy was administered as follows First corticotropin was given intramuscularly for three days (June 19 to 21) in daily doses of 60 units This was followed by cortisone intramuscularly for the next 26 days in varying doses as indicated Treatment was interrupted for seven days (July 18 to 24) and then in an attempt to suppress the carditis more effectively corticotropin was reinstituted in higher dosage first in daily doses of 200 units then 300 and later 160 units After 31 successive days the drug was withdrawn As will be seen in Figure 35 soon after the hormone was stopped the temperature and E S R rose and the C R P reappeared Without further treatment however these clinical

Abdominal distention is another undesirable effect seen more frequently in children, particularly those younger than 8 years Distention appears as early as the first week but more frequently during the second or third week of cortisone or corticotropin administration (Figure 34) It regresses slowly and does not completely disappear until several weeks after treatment is terminated

It is noteworthy that none of the children or adolescents in our series developed those more serious undesired effects seen in adults, such as mental changes, peptic ulcer or bone fracture

The Rebound Phenomenon

Within 3 to 14 days after cortisone is withdrawn the majority of patients whose signs and symptoms of rheumatic fever have disappeared will exhibit a transitory relapse or rebound, i e a recrudescence of one or more clinical or laboratory manifestations present prior to therapy (Table 24) The duration of a transitory clinical relapse consisting of fever tachycardia or polyarthritis ranges from one to two weeks A "laboratory rebound," such as reappearance of C R P secondary rise in E S R or recurrence of P R interval prolongation, may last from one to three weeks (C R P) or even up to five weeks (E S R) Usually a rise in antistreptolysin O titer (A S O) does not occur during the rebound The incidence of these phenom

Table 24

Incidence Nature and Duration of Rebound Phenomena

Attack of Rheumatic Fever	*No of Patients Treated*	*No Showing Rebound Phenomena*		
			Interval from onset of illness to institution of treatment (days)	2-10)
Initial	29	21	Average period of treatment (weeks)	6
Recurrent	9	7		
Total	38*	28	Interval between cessation of treatment and onset of rebound (days)	3-14†

Nature of Rebound Phenomena	*Number of Cases*	*Duration (weeks)*
Secondary rise in E S R	26	1-5
Reappearance of C R P	16	1-3
Rise in temperature	J	1-2
Return of tachycardia	9	1-2
Reappearance of polyarthritis	6	1-2

E S R = Erythrocyte Sedimentation Rate C R P = C Reactive Protein

* Six patients have not been included in this tabulation because two were inadequately treated two could not be followed properly one had persistent rheumatic activity during and after treatment and one had a polycyclic course

† One patient exhibited rebound 21 days after cessation of treatment

Therapy

Dosage and Duration of Treatment Cortisone should be given as soon as the indications for its use appear The oral preparation should receive preference because it is simple to administer and is well tolerated When given by mouth cortisone is absorbed more rapidly and is not less effective than when injected intramuscularly The daily oral dose should be divided into three or four equal parts and administered at approximately equal intervals

Enough cortisone should be given to suppress satisfactorily the signs and symptoms of the disease In children the pulse rate taken while the patient is asleep is an especially useful gauge of adequacy of dosage The amount given should not be related to age or weight but to the severity of the disease and the responsiveness of the patient Children usually require the same dosage as adults

In general it has been found advisable to start with a higher dosage and reduce it gradually In the average case the following schedule is recommended 300 mg the first day 200 mg daily for the next 5 to 10 days and 100 mg for the following 2 to 4 weeks Provided the signs of activity are adequately suppressed the daily dose may then be decreased by 25 mg each successive week Greenman and his associates[18] recommend 300 mg of cortisone daily for six weeks and decreasing amounts for the following two weeks

It has become conventional to administer cortisone to patients with rheumatic fever for approximately six weeks In treating an individual patient it is wiser to administer the hormone as long as the carditis remains moderately severe and responds favorably to therapy than to adhere to any fixed schedule Barnes and his associates[17] recommend that treatment be maintained until the disease has reached the end of its natural course

Indications for Retreatment Reappearance of signs of rheumatic activity may not indicate relapse or recurrence but may represent a rebound phenomenon as previously discussed When however signs of moderate or severe carditis recur and show no tendency to subside spontaneously after one or two weeks a second course of cortisone should be instituted The duration of this course should be governed by the same principles as the initial course

Diet and Potassium Salts During the administration of cortisone sodium chloride in the diet of all patients with rheumatic fever should be restricted to 1 0 Gm daily If there is a tendency to retain sodium or water or if congestive failure is present or imminent sodium intake should be further reduced to 50 mg daily Patients should be weighed every one to two days

Potassium chloride in enteric coated tablets 1 0 Gm two or three times daily after meals should be given while the patient is receiving 100 mg or more of cortisone daily

and laboratory changes returned to normal It will be noted that the A S O titer was unaffected by either the administration or withdrawal of the hormone

Indications and Contraindications

As the mechanism of action of cortisone and corticotropin and the pathogenesis of rheumatic fever are not known the rationale of or the indications for employing cortisone in the treatment of this disease must depend largely upon clinical results thus far achieved by its use Polyarthritis fever and toxicity respond quite dramatically *to salicylates hence the hormones do* not seem to be indicated in cases of acute rheumatic fever not complicated by carditis If however future studies should demonstrate that the hormones have the capacity to prevent damage to cardiac structures when administered before the development of carditis then of course cortisone would be indicated in such cases At present however there is no conclusive evidence that cortisone or corticotropin possesses such attributes

Cortisone is most valuable in acutely ill patients with carditis especially when it is associated with pericarditis or congestive failure because the hormone controls the acute symptoms rapidly and usually produces general improvement in the patient's condition Signs of congestive failure may disappear without digitalis or diuretics Cortisone is unquestionably indicated when the patient is critically ill and the outcome appears uncertain In mild carditis without pericarditis or congestive failure and without evidence of progression of the disease use of the hormone is optional Some workers have suggested combined hormonal and salicylate therapy This combination is not contraindicated since the agents are not mutually antagonistic In mild or moderately severe chronic carditis of long duration (months to years) cortisone is not usually effective

There is no evidence as yet that cortisone is unequivocally helpful in chorea Its use in simple uncomplicated chorea would therefore be exploratory

Cortisone is not indicated in inactive rheumatic heart disease or in congestive failure not associated with active carditis

In cases of subacute bacterial endocarditis associated with active rheumatic carditis when use of the properly selected antibiotic as the sole agent *fails to control the disease cautious administration of cortisone* combined with the antibiotic may be tried

In the presence of active tuberculosis administration of cortisone may be hazardous The coexistence of this infection should be searched for before during and after hormonal therapy A healed tuberculous lesion is not a contraindication if use of the hormone is warranted by the degree of rheumatic activity in the individual patient Since however such apparently inactive tuberculous foci may be reactivated it is essential that roentgenographic observations be made during hormonal therapy and for a period of time after its cessation If active tuberculosis is present and the use of cortisone is clearly indicated streptomycin and *p* aminosalicylic acid should be given with the hormone [21]

Other contraindications are discussed elsewhere in this volume

the capacity to overcome the disease For patients who are critically ill the hormone appears to be lifesaving

Comparative Evaluation of Cortisone and Salicylates

Before the advent of cortisone the effects of salicylates upon the temperature and upon polyarthritis were described as dramatic So spectacular and uniform is their effect upon articular inflammation that for many years salicylates have been used as a therapeutic-diagnostic test for the polyarthritis of rheumatic fever Many observers were of the impression however that salicylates exerted little influence on the progress course or sequelae of active rheumatic carditis

Precisely what are the relative merits of the salicylates as compared to the adrenocortical hormone? This is the question which the international cooperative study by the Council on Rheumatic Fever of the American Heart Association and the British Medical Research Council has been designed to answer In June 1952 a preliminary report of their findings based upon analysis of less than half the total cases stated It appears that individual symptoms signs or laboratory observations may have been affected more favorably by one or another of these 3 drugs (cortisone corticotropin and salicylates) but no consistent pattern is evident No firm conclusions can at present be drawn concerning the drug most effective in the control of the acute illness The cases have not been under observation sufficiently long to provide data on the prevention of rheumatic heart disease

In our limited experience an unusual opportunity to compare the effects of cortisone with aspirin in the same patient was presented in the case of a boy who had a severe prolonged initial attack of rheumatic carditis

CASE REPORT

Sixteen days before admission the patient a boy of 10 had pharyngitis and twelve days later complained of fever and arthralgia On admission his temperature was 103 2 F and a soft blowing apical systolic murmur was heard The E S R was markedly elevated and the C R P strongly positive Within 48 hours the murmur became harsh and well transmitted a gallop rhythm appeared and electrocardiographic changes indicative of pericarditis developed although no friction rub was audible Aspirin was begun on the fourth hospital day An apical mid diastolic murmur appeared on the fourth day and pericardial friction rub on the eighth day of therapy By the tenth day after admission the A S O had risen from 375 to 760 units per cc of serum As will be noted in Figure 36 no reduction in the E S R or disappearance of the C R P occurred despite the high doses of aspirin Clinically there was slow and slight improvement Aspirin was discontinued after six weeks The temperature then rose to 104 6 F and the pericardial friction rub was again heard The rhythm became totally irregular and was nodal in origin The heart sounds were distinctly poorer in quality than at the beginning of therapy and both systolic and diastolic apical murmurs became louder and harsher The patient was critically ill Five days after aspirin was discontinued oral cortisone therapy was instituted and striking improvement followed The rhythm became regular and the quality of heart sounds improved Within 48 hours the pericardial friction rub disappeared The sleeping pulse rate which was 124 per minute the night before cortisone was first given fell to 72 on the ninth day and the temperature became normal For the

Supplementary Antimicrobial Therapy

It is important to eradicate hemolytic streptococci from the pharynx and nasopharynx of patients with rheumatic fever and to protect these patients from streptococcal reinfection Immediately after the patient comes under observation 300 000 units of procaine penicillin G in 2 per cent aluminum monostearate should be given intramuscularly This should be repeated every three days for a total of four doses In addition, sulfadiazine 0 5 Gm daily to children weighing less than 60 lbs and 1 0 Gm daily to those who weigh more should be given orally in single doses beginning 14 days after starting cortisone therapy It is important that following treatment of the active disease the patient be maintained on an effective prophylactic regimen of penicillin or sulfadiazine

Recommended Procedures

The following procedures are suggested as a minimum requirement for adequate observation and care of the patient selected for hormonal therapy

Prior to Therapy (1) X ray of chest (2) electrocardiogram (3) blood pressure (4) E S R (5) fasting blood sugar (6) complete blood count (7) urinalysis

During and After Therapy All the procedures listed should be repeated every two weeks during the period of hormone administration Those which reveal abnormal findings should be performed at weekly interval All tests done prior to therapy should be repeated at weekly intervals for a total of four weeks after the drug is discontinued irrespective of whether clinical manifestations of rheumatic fever reappear

Evaluation of Cortisone Therapy

Cortisone is effective in reducing to normal with a fair degree of consistency and quite rapidly the temperature resting pulse rate E S R C R P plasma fibrinogen and serum gamma globulin Within a few days after cortisone therapy is begun there is pronounced improvement in the well being appetite and emotional state of the patient and polyarthritis disappears

The effect of cortisone upon carditis however is difficult to assess The role of the hormone in suppressing the inflammatory process and in retarding reducing inhibiting or preventing proliferation is at present obscure It is doubtful that cortisone significantly shortens the natural course of the disease It is evident that the hormone is not capable of terminating active rheumatic carditis and it certainly is not a cure for rheumatic fever Whether or not cortisone can prevent damage to cardiac structures remains to be seen

Yet congestive failure the most serious complication of carditis often responds favorably, as does pericarditis At the bedside of a patient severely ill with rheumatic fever one gains the impression that cortisone enhances

and the heart sounds were no longer overactive Cortisone was discontinued after 10 weeks During the second and third weeks after hormone withdrawal the E S R rose moderately but the C R P test remained negative However 21 days after cortisone was stopped the temperature increased to 102 8 F the pulse quickened to 120 per minute and the C R P again became positive The diastolic murmur did not reappear During the following eight days the abnormal signs disappeared spontaneously and the disease has since remained inactive This evidently was an unusually delayed rebound phenomenon

The superiority of cortisone to aspirin in its effect upon cardiac as well as systemic manifestations in this patient is demonstrated in Figure 36 It must not be inferred however that the difference between the response to the two agents as illustrated by this single case is representative or would necessarily obtain in other cases similarly treated

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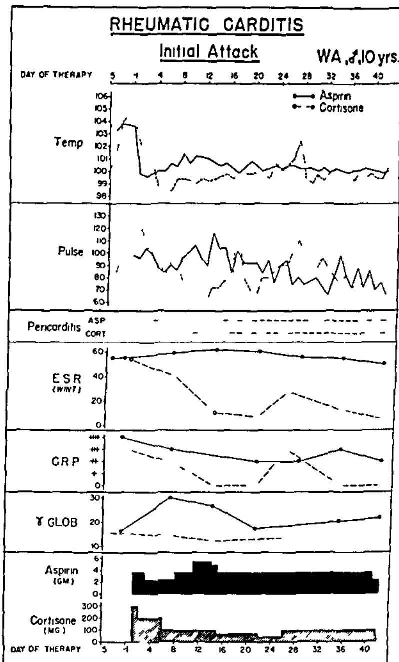


Fig 36 Comparison of the effects of aspirin and corti one u ed during a severe prolonged initial attack of rheumatic carditis

first time during the patient s illness the E S R and the C R P tests returned to normal These laboratory changes were noted on the fourteenth day of cortisone therapy When however reduction of corti one dosage reached 50 mg daily the temperature pul e rate and E S R increa ed and the C R P reappeared in the serum Upon restoring the daily dose of 100 mg improvement was again induced By the eighth week of cortisone therapy the apical diastolic murmur had di appeared

and the heart sounds were no longer overactive Cortisone was discontinued after 10 weeks During the second and third weeks after hormone withdrawal the E S R ro e moderately but the C R P test remained negative However 21 days after cortisone was stopped the temper iture increased to 102 8 F the pulse quickened to 120 per minute and the C R I agun became positive The diastolic murmur did not reappear During the following eight days the abnormal signs di appeared spontaneously and the disease has since remained inactive This evidently was an unusually delayed rebound phenomenon

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5

Other Collagen Diseases

George Baehr and Marvin F Levitt

A number of diseases characterized by conspicuous changes in the collagen (or binding tissue) of the body have been grouped in recent years as diseases of collagen This is not intended to suggest that they have a common pathogenesis but rather that they all demonstrate specific alterations in the connective tissue Connective tissue which consists of fibroblasts collagen and ground substance can react to injury in limited fashion It may manifest necrosis or if the injury is less intense fibrinoid degeneration cellular proliferation and infiltration and tissue sclerosis Accordingly a wide variety of irritating stimuli may produce identical alterations in the collagen fibers [1,2] Fibrinoid degeneration of the collagen as one specific example may be induced locally by the phenomenon of Arthus may represent a prominent feature in generalized allergic inflammations or may appear at the base of peptic ulcers in the walls of arterioles in malignant hypertension in low grade infections and adjacent to foreign bodies

Although the common pathologic alterations do not constitute reliable evidence for common pathogenesis they explain the clinical similarities between these diseases Collagen tissue serves as a binding framework in the synovial and serous membranes the endocardium and the walls of the blood vessels and its alteration at these sites accounts for the fact that such clinical manifestations as arthritis polyserositis and scattered vascular lesions are common to all the diseases of this category Nevertheless each member of this disease group represents a distinct entity with the specific manifestations reflecting the particular tissue response as well as the distribution of the pathologic lesion

That cortisone and corticotropin may dramatically suppress many of the clinical manifestations of the diseases of this group[3] provides additional

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This chapter is an extension and amplification of the senior author s article Disseminated Lupus Erythematosus in Cecil and Loeb s *Textbook of Medicine* 8th edition 1951 published by W B Saunders Company Philadelphia

support for classifying them together It should be reemphasized, however, that this qualitative similarity in response to these hormonal agents does not imply *similar etiology but rather similar pathologic reactions*

In this chapter the four diseases which will be discussed are usually included with rheumatoid arthritis and rheumatic fever in this heterogeneous group (1) disseminated lupus erythematosus, (2) polyarteritis (3) diffuse scleroderma, (4) dermatomyositis

Disseminated Lupus Erythematosus

Definition Among the heterogeneous group of collagen diseases disseminated lupus erythematosus constitutes a disease entity distinguished by a prolonged clinical course which usually terminates fatally by a predilection for young females and by characteristic pathologic changes in the collagenous tissues changes which affect especially the vascular system and the serous and synovial membranes [4,5] Because in many instances an erythematous rash is apt to appear on the face and other parts of the body at some stage of the disease the condition was first described about the middle of the nineteenth century by dermatologists (Hebra Casenave, Kaposi) who named it *lupus erythematodes* or *erythematosus* In spite of its name, this disease bears no relationship to tuberculosis and lupus vulgaris nor to that benign indolent skin lesion known to dermatologists as *discoid lupus erythematosus*

Incidence One of the characteristics of the disease is its predominance among young females 22 out of 23 cases reported by Baehr Klemperer and Schifrin[4] in 1935 occurred in females the vast majority in the second and third decades of life More recent experience however indicates that males may constitute 15 to 25 per cent of all cases and that despite a predominant occurrence in young adults the subjects may range in age from 3 to 60 years During the past 18 months we have encountered 5 patients with fairly typical disseminated lupus erythematosus between the ages of 3 and 15

Etiology Bacteriologic studies have as yet revealed no clue concerning the cause of this disease Blood cultures are negative unless there is an intercurrent pneumonia or a terminal streptococcus or staphylococcus blood infection There are as a rule no clinical or other evidences of allergy Although more than 75 per cent of the patients are female no endocrine disorder is recognizable in either sex

Pathology At the autopsy table the frequent paucity of gross anatomic changes presents a striking contrast to the profound systemic manifestations leading to the death of the patient The widespread and heterogeneous visceral lesions usually revealed by microscopic study can be ascribed to alteration in the ground substance and collagen fibrils of the connective tissues of the body which are especially conspicuous in the walls of small blood vessels and beneath synovial and serous membranes

Pericardial and pleural involvement occurs frequently and may appear as a thick, gelatinous connective tissue matrix completely obliterating the

serous space This appearance is caused by a series of proliferative and degenerative changes of the collagenous tissue underneath the mesothelium Perisplenitis and perihepatitis are likewise common

In about 30 per cent of the cases examined grossly the endocardium of one or more valves exhibits a pathognomonic lesion first described by Libman and Sacks[6] as *indeterminate endocarditis* to distinguish it from vegetations due to known bacteria The endocardial vegetations may be small and verrucous or large broad and flat They may occur on either side of the valvular leaflets *sometimes also on the chordae tendineae or the mural* endocardium of the ventricle Microscopically the lesion begins as a fibrinoid degeneration or necrosis of the connective *tissue fibrils and a swelling of the* ground substance immediately beneath the endocardium A subendothelial accumulation of collagenous material develops which protrudes as an excrescence on the surface of the endocardium In the terminal period of the disease, such advanced endocardial vegetations may occasionally become infected secondarily with bacteria (secondary acute or subacute bacterial endocarditis)

Focal lesions of the interstitial collagenous tissue of the myocardium morphologically identical with those seen in the endocardium and pericardium are *present in about 35 per cent of the cases Aschoff bodies are not* found

The small arteries and arterioles of various viscera especially of the kidneys may show fibrinoid degeneration and necrosis of the connective tissue matrix of the vessel wall [7] This may lead to a reactive proliferation of the lining endothelium and to a thrombotic occlusion of the affected arterioles The renal glomeruli may show focal necroses of occasional loops or the walls of some glomerular capillaries may be thick rigid deeply eosinophilic— the so-called wire loop lesion [8] These alterations are merely another expression of the widespread damage to subendothelial collagen

The spleen is usually not markedly enlarged unless there is an intercurrent secondary bacteremia Microscopically the central arteries of the malpighian lymph follicles are surrounded characteristically by conspicuous concentric rings of connective tissue

Erythematous areas of skin may show very few microscopic changes except capillary dilatation small red cell extravasations edema and some swelling of the ground substance between connective tissue fibrils Older lesions may show fibrinoid degeneration of the collagenous tissues of the upper corium and of small blood vessels but *microscopic examination of a* small biopsy specimen is often disappointing

The regional lymph nodes are usually enlarged during periods of exacerbation and on biopsy they sometimes show areas of necrosis Bronchopneumonia is a frequent terminal complication

Pathologic Chemistry The swelling and fibrinoid degeneration of the collagen fibrils which may melt into more or less homogeneous metachromatic intercellular masses *represent the characteristic pathologic* alteration in disseminated lupus erythematosus Within these masses deeply purplish

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istically irregular erythematous macules are seen on the tips of the fingers the thenar and hypothenar eminences the palms and even the tips of the toes and the balls and heels of the feet Actually any area exposed to rubbing or other mechanical trauma such as the bony prominences (elbows knees shoulders malleoli buttocks and the dorsal aspects of the forearm) may reveal the typical changes The appearance of an erythema spreading across the bridge of the nose and the malar eminences in a patient suffering from fever and other systemic manifestations greatly facilitates the diagnosis It should be emphasized however that the typical rash is present in only 50 per cent of the patients and that even in its absence the other clinical manifestations should be adequate for diagnosis On the other hand an erythema in the expected location does not per se warrant the diagnosis of disseminated lupus erythematosus

If the rash has existed for some time minute telangiectases may be scattered in the midst of the erythema as evidence of permanent vascular change Small groups of purpuric and petechial hemorrhages are sometimes seen on the skin and mucous membranes at the height of the disease All the skin manifestations are especially prominent during an acute exacerbation often with an intense violescent erythema During the periods of remission the erythematous skin reaction may subside and be replaced by areas of brown macular pigmentation In some patients the onset of typical skin lesions or of other systemic manifestations of lupus erythematosus follows exposure to the sun Patients who have had a low grade fever and arthralgias for weeks or months often suffer an acute exacerbation following such solar exposure At the height of the disease erythematous and petechialike lesions may appear on the mucous membranes particularly the mouth lips and soft palate These lesions may develop into shallow ulcers surrounded by a hemorrhagic or intensely erythematous areola

When the fever is high and the patient extremely toxic tachycardia with gallop rhythm usually is present The electrocardiogram frequently reveals low voltage and in this event signs of pericarditis The pulmonic second sound is usually pronounced and systolic blowing murmurs are often heard If the systolic murmur becomes particularly rough and conspicuous it may indicate the presence of an underlying atypical verrucous endocarditis (Libman Sacks disease) which develops in the advanced stage in about 30 per cent of the patients

Electroencephalographic tracings are frequently abnormal during an acute exacerbation Occasionally the cerebrovascular changes may induce an organic psychosis and the combination of mental confusion disorientation and hallucinations may mask the clinical picture Generalized and focal convulsive seizures may occur during the terminal exacerbation of the disease

A generalized lymphadenopathy is common The spleen is palpable in about 20 per cent of the patients but only rarely is it markedly enlarged Ophthalmoscopic examination frequently reveals characteristic evidence of vascular injury perivascular hemorrhages fluffy exudates, segmentation of arteries and at times even papilledema

staining material may sometimes be found, the pathognomonic hematoxylin bodies which have been identified by Klemperer et al [9] as depolymerized desoxyribonucleic acid Presumably the same abnormal chromatin, ingested by leukocytes produces the specific L E cell described by Hargraves Richmond and Morton [10] These findings suggest that increased nucleoprotein breakdown may represent the fundamental chemical disturbance in disseminated lupus erythematosus The conspicuous and characteristic increase in serum hexosamine [11] believed to be derived from the mucoprotein of the altered ground substance may likewise reflect increased protein degradation That disseminated lupus erythematosus is associated with a specific disturbance in cellular nucleoprotein chemistry appears likely but the precise enzymatic defect remains to be established

Symptoms The salient clinical manifestations are (1) prolonged irregular fever with a tendency to remissions of variable duration (2) a tendency to recurrent involvement of synovial and serous membranes (polyarthritis, pleuritis pericarditis) (3) depression of bone marrow function (leukopenia moderate hypochromic anemia and thrombocytopenia) and (4) evidences of vascular alterations in the skin retina kidneys, and other viscera

In the absence of the rash the clinical picture may simulate an infectious polyarthritis The pain and swelling of the various joints may be so conspicuous as to render it difficult to distinguish this disease from rheumatic fever or rheumatoid arthritis Alternatively the joint symptoms may appear as recurrent arthralgias and prominent joint stiffness with few objective findings In most subjects fever joint symptoms leukopenia and microscopic hematuria comprise the essential clinical manifestations of the underlying disease

Suspicion that the illness is not rheumatic fever or rheumatoid arthritis is warranted whenever abnormal urinary findings appear Microscopic hematuria and mild albuminuria are almost universal findings Much less frequently the albuminuria may be massive and associated with edema hypertension and even renal insufficiency and progressive azotemia In such patients the picture may closely resemble the nephrotic or nephritic form of chronic glomerulonephritis These examples of severe renal damage represent irreversible vascular changes and usually occur in the advanced stage of the disease Occasionally however the renal findings predominate throughout the clinical course

In addition to arthralgias and arthritis attacks of pleurisy or pericarditis may occur during exacerbations of the disease In some patients severe abdominal pain secondary to peritonitis or perihepatitis and perisplenitis may simulate an acute condition requiring surgical procedure

Either at the onset or sometimes at a later stage vascular lesions become visible on the skin as erythematous macules or patches which tend to become confluent The rash first appears as a rule on the more exposed parts of the face the bridge of the nose and cheeks above the eyebrows on the upper lip, the prominence of the chin and the edge of the pinna It is also commonly found on the V shaped exposed area of the upper chest Character

spontaneous remission In some cases complete remission may last for years but the ultimate prognosis is grave Occasionally a patient who has been critically ill for months may improve slowly, and ostensibly recover completely Most untreated patients ultimately die however in an exacerbation of the disease Death is most commonly caused by the toxemia of the disease renal insufficiency or an intercurrent pneumococcus streptococcus or staphylococcus infection Cortisone and corticotropin although they do not alter the ultimate prognosis have been effective in controlling the clinical manifestations of the disease and in improving the strength and well being of these patients

Polyarteritis

Definition Polyarteritis (periarteritis nodosa) is a progressive usually fatal disease of protean manifestations secondary to inflammatory disease of the walls of medium and small sized arteries The disease owes its name to the appearance in some cases of gross aneurysmal dilatations of the weakened arteries It was first described as a pathologic entity in 1886 by Kussmaul and Maier who considered the most likely cause to be trichinosis Kling quoted by Klemperer focused attention upon the fibrinoid degeneration in the walls of the blood vessels a characteristic change which helped to classify this disease among the diseases of collagen

Incidence Most descriptions of this disease emphasize its multitude of *clinical manifestations affecting various organs and tissues and the rarity of* correct diagnosis during life There are however approximately 350 well-documented cases described in the literature and antemortem diagnosis is becoming much more frequent Males afflicted with the disease outnumber the females in a proportion of two to one No age group is spared and the reported cases range in age from 4 to 71 although the average age of onset is about 37 The most frequent occurrence is in the third and fourth decades of life

Etiology In most cases the etiology is unknown Because of a frequent history of a preceding streptococcal infection an altered reactivity to the streptococcus has been implicated by some authors The relation to the streptococcus remains unproved Fresh Aschoff bodies were seen in some cases of polyarteritis by Friedberg and Gross in 1934 The relation between the rheumatic process and polyarteritis however is probably based upon similar pathologic alterations in a common tissue rather than upon a common etiology More recently some have considered polyarteritis to be an advanced stage of a vascular allergy or of a hyperergic vascular response the symptoms of which depend upon the specific shock organ involved Of the patients with this disease 18 to 25 per cent have a previous history of bronchial asthma or atopic skin reactions and vasomotor rhinitis [17] In one series 70 per cent of the youngest patients with polyarteritis had severe asthmatic symptoms [18] Rich and Gregory[19] described 5 patients who had been sensitized with foreign serum and subsequently developed a fatal form of serum sickness in whom necropsy revealed a necrotizing arteritis Rich[20]

The combination of a leukopenia of 3 500 to 5 000 cells with a mild shift to the left a secondary anemia of about 60 to 70 per cent, and a thrombocytopenia suggests the possibility of disseminated lupus erythematosus in a patient with fever and joint symptoms The characteristic leukopenia may be replaced temporarily by leukocytosis when a secondary infection such as pneumonia occurs The anemia is usually moderately severe unless renal insufficiency supervenes in which case it may be marked and normochromic Occasionally a hemolytic process associated with a positive Coombs' test and circulating autohemolysins may exaggerate the severity of the anemia Moderate thrombocytopenia is characteristic It may occasionally be so marked as to produce purpuric manifestations indistinguishable from those of idiopathic thrombocytopenic purpura In several patients splenectomies have been mistakenly performed The spleen may be particularly enlarged in these hematologic forms of disseminated lupus erythematosus

In 1948 Hargraves Richmond, and Morton[10] described what they believed to be pathognomonic L E cells in stained bone marrow smears from patients with disseminated lupus erythematosus These cells are phagocytes usually polymorphonuclear leukocytes containing masses of purplish staining chromatin material which typically fills the entire cell and pushes the nucleus to an eccentric position The cells are found in the heparinized marrow smear or in the buffy coat of peripheral blood if properly heparinized and incubated They may also be induced in normal marrow or peripheral blood following their incubation with the plasma from patients with active disseminated lupus erythematosus Klemperer et al[9] have demonstrated that this phagocytosed material represents depolymerized desoxyribonucleic acid implying that it derives from products of nuclear degeneration The desoxyribonuclease inhibitor present in normal white cells inhibits the L E cell phenomenon,[12] which confirms Klemperer's observation We have found these cells remarkably specific for the diagnosis of disseminated lupus erythematosus despite scattered reports[13] of their alleged presence in a few patients with amyloidosis atypical anemia and tuberculosis In those patients in whom the clinical picture is obscure and not clearly differentiated from rheumatoid arthritis chronic nephritis Hodgkin's disease or even a primary anemia the finding of L E cells has proved of real value in defining the true diagnosis

During exacerbations of the disease the serum concentration of total proteins may be markedly elevated The typical electrophoretic pattern as demonstrated by Coburn and Moore[14] and by Peiner[15] consists of a decrease in the serum albumin and an increase in the alpha 2 and gamma globulins The latter may in part be responsible for the falsely positive blood Wassermann and for the very rapid erythrocyte sedimentation rate (E.S.R.) Haserick, Lewis and Bortz[16] demonstrated that the gamma globulin factor is specifically involved in the production of the L E cell Anti-gamma globulin inhibits the formation of these cells

Prognosis The fever and other manifestations of the disease may continue for many months, with long alternating periods of exacerbation and

spontaneous remission In some cases complete remission may last for years but the ultimate prognosis is grave Occasionally a patient who has been critically ill for months may improve slowly and ostensibly recover completely Most untreated patients ultimately die however in an exacerbation of the disease Death is most commonly caused by the toxemia of the disease renal insufficiency or an intercurrent pneumococcus streptococcus or staphylococcus infection Cortisone and corticotropin although they do not alter the ultimate prognosis have been effective in controlling the clinical manifestations of the disease and in improving the strength and well being of these patients

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demonstrated that there had been a marked increase in the frequency of polyarteritis coincident with the advent of the sulfa drugs Vascular reactions of the type seen in polyarteritis have been produced in rabbits by bacterial and serum sensitization Similarly, animals treated with sulfa and serum have shown identical lesions Harkavy[21] believes that the process is reversible if the responsible antigen is removed Although some patients present a clear cut allergic background (manifested by the recent onset of asthma atopic sensitization or significant eosinophilia) a specific allergic factor cannot be demonstrated in most of the patients

Pathology The fundamental lesion in polyarteritis is a necrotizing inflammatory obliterative process involving small arteries, arterioles, and occasionally veins The pathologic process has been divided into progressive stages

1 The first stage is one of edema and fibrinoid eosinophilic necrosis of the inner media subendothelial tissues and usually the adventitia

2 Coincident with this fibrinoid necrosis there is an infiltration of the adventitia and media with inflammatory cells among which neutrophils usually predominate although eosinophilic infiltration may be prominent Later in the process mononuclear cells usually replace the polymorphs

3 The endothelium is often destroyed with subsequent thrombosis and tissue infarction These changes are particularly frequent in the kidneys intestines liver spleen and myocardium Thrombosis is usually followed by organization and frequently by recanalization of the occluded vessels

4 In the healing stages the inflammatory lesions of the affected vessel walls are replaced by an intense arterial and periarterial fibrosis

Grossly the multiple occurrence of nodose lesions (2 to 4 mm in diameter) along the course of the small arteries is a characteristic but not an essential feature This nodosity may result from granulomatous proliferation or aneurysm formation of arterial walls secondary to the medial necrosis Usually there is involvement of blood vessels in many organs the frequency of organ involvement being kidneys 87 per cent heart 84 per cent liver, 71 per cent spleen 31 per cent lungs 25 per cent [2] After a prolonged clinical course each organ usually demonstrates the complete range of arterial lesions from the early arterial necrosis and cellular infiltration to the later healing periarterial fibrosis

Symptoms The clinical picture may present a bewildering complex of symptomatology attributable to the circulatory disturbances in various regions of the body The cardinal features of the clinical appearance are usually fever weakness and prostration conspicuous leukocytosis with a shift to the left frequently associated with marked eosinophilia, albuminuria and microscopic hematuria abdominal pain signs and symptoms of polyneuritis, hypertension

The onset is usually insidious with fever and malaise Often persistent fever follows a mild respiratory or sinus attack without an intervening period of good health The variety of symptoms their distribution among various

organs and tissues of the body and the obvious severity of the disease are suggestive of diffuse polyarteritis. Certainly the presence of an unexplained fever and leukocytosis with recurrent arthralgias and vague muscle aches coupled with the involvement of unrelated organs should suggest the nature of the underlying disease.

Renal involvement, consisting of mild to moderate albuminuria, microscopic hematuria, and cylindruria, is almost a constant finding.[3] In some patients these findings associated with a generalized edema often suggest the diagnosis of glomerulonephritis. Three quarters of the patients suffer from progressive hypertension. The presence of persistent fever, leukocytosis, and eosinophilia, and the involvement of nonrelated organs and of peripheral nerves preclude the diagnosis of glomerulonephritis. In its terminal stage the disease may be characterized by intractable hypertension associated with increasing renal insufficiency and may resemble malignant hypertension.

Myocardial involvement secondary to coronary arteritis may produce signs and symptoms indistinguishable from those of arteriosclerotic heart disease. Pericarditis with a pericardial rub may result from a myocardial infarction, from a periarteritic involvement of a coronary artery, or from a hemorrhage into the pericardial sac. The electrocardiographic findings usually consist of nonspecific T wave changes, although the picture of acute pericarditis or frank coronary occlusion may also be seen. In any event, the symptoms of cardiac involvement may range from typical angina to prolonged chest pain and even severe congestive heart failure.

Although it was originally felt that the lungs are generally exempt from the lesions of polyarteritis, about 40 per cent of the patients suffer from arterial involvement of the pulmonary system. Actually in some patients the pulmonary findings may predominate. In such instances the combination of fever, marked eosinophilia, dry hacking cough, and fleeting and diffuse pulmonary infiltrations all suggest the diagnosis of Loeffler's syndrome. Only the persistence of the pulmonary symptoms and the subsequent development of other signs of diffuse vascular involvement reveal the true nature of the disease process. In a significant proportion of the described cases a history of bronchial asthma precedes the onset of more extensive vascular involvement. Likewise in many patients with active polyarteritis, the symptoms of intractable asthma may dominate the clinical picture with or without X ray evidence of pulmonary involvement.

Occasionally the presenting complaints are referable to the gastrointestinal tract.[4] There may be persistent abdominal pain, anorexia, and vomiting. Vascular involvement of the gallbladder or appendix with consequent infarction and necrosis may compel surgical exploration. Not infrequently the first hint of the diagnosis is suggested by the pathologist's examination of the offending gallbladder or appendix. Hemorrhagic pancreatitis, retroperitoneal bleeding, and perforated small intestinal ulcers may all result from gastrointestinal polyarteritis. Vascular involvement of the liver may produce focal areas of hepatic necrosis, subcapsular hemorrhages with symptoms of right upper quadrant tenderness and icterus, and signs of hepatic enlargement.

and deranged liver function tests Splenomegaly, though rarely conspicuous is present in about 10 per cent of the patients

Symptoms of polyneuritis play a conspicuous role in about one third to one half of all the patients involved They include peripheral hyperesthesias numbness tingling and sometimes foot drop and usually result from the arteritic process in the nutrient vessels to the spinal cord or the peripheral nerves Symptoms of central nervous system ischemia—such as convulsions coma, meningeal signs and vascular accidents—also occur, but far less frequently

About 20 per cent of the patients suffer from a wide diversity of cutaneous manifestations These reactions may vary from mild recurrent urticarial lesions to generalized lentil shaped nodules which may break down and ulcerate Not infrequently the most overt signs of the disease are hemorrhagic extravasations into the skin and subcutaneous tissue which eventually coalesce and slough producing large necrotic ulcers Purpuric manifestations may also mimic the picture of Schonlein Henoch purpura Marmoration of dependent skin areas secondary to venous stasis may be particularly conspicuous in polyarteritis The small nodose lesions along the course of the arteries from which the disease derives its name are only rarely palpable

The usual hematologic findings consist of a leukocytosis with a very distinct shift to the left and a rapid E S R The white blood count usually varies from 15 000 to 30 000 although normal white blood counts and even leukopenias have been described There is usually only a mild secondary anemia Eosinophilia may approach 40 to 60 per cent of the total white blood count, it is absent in some cases

Occasionally the disease may terminate fatally within two to four weeks though the clinical course may be prolonged for months or several years Often a clinical suspicion may be confirmed by skin and muscle biopsy but an inconclusive pathology report does not exclude the diagnosis Another laboratory finding which sometimes proves helpful is the presence of a markedly elevated trichinella agglutinin titer which appears to be nonspecific

In our experience we have not observed a single patient with necrotizing polyarteritis in whom L E cells have been demonstrated A long standing or even more recent allergic background as well as the history of a bizarre response to sulfa ingestion also favors the diagnosis of polyarteritis

Prognosis The prognosis is extremely poor and many patients succumb to progressive renal or cardiac insufficiency or intercurrent infection within 12 to 18 months Although some have claimed that those patients with a demonstrable allergic etiology may be cured by removal of the sensitizing antigen this has not been our experience

Diffuse Scleroderma

Definition Diffuse scleroderma is a chronic progressive disease affecting the collagenous portion of the connective tissue the chief manifestation of which is a peculiar hardening induration and rigidity of the skin Similar changes are found in the collagenous tissue of the subcutaneous tissue mus

cles tendons, and viscera (In this chapter, the term *scleroderma* refers to diffuse scleroderma The circumscribed type of scleroderma which affects only the skin and subcutaneous tissues is unrelated to the diffuse form and should not be treated with cortisone or corticotropin)

Incidence The disease affects women predominantly the proportion of female to male patients being approximately two to one Cases have been described from infancy to old age but the onset typically occurs in the third to fifth decade of life Despite the relative infrequency of the disease several members of the same family may exhibit typical skin changes

Etiology The specific cause of scleroderma is not known but many hypothetic etiologic factors have been suggested [6] The onset of the typical skin changes is sometimes preceded by an acute infection No single infectious agent however has been etiologically related to a significant proportion of the cases Some have implicated rheumatic fever because cases have been described in which signs of rheumatic carditis and scleroderma coexist Other observers believe that the typical fibrotic changes represent trophic sequelae of primary disorders of the nervous system The presence of symmetrical degeneration of the nerve cells of the dorsolateral columns of the spinal cord is cited as evidence for this point of view [7]

A wide variety of endocrine disturbances has likewise been noted in scattered cases In some patients atrophy of the thyroid gland is prominent others have developed symptoms of scleroderma after treatment with thyroid hormone The rapid emaciation and cachexia often suggest pituitary hypofunction and indeed atrophy of the anterior pituitary has been demonstrated on occasion The adrenal gland has been implicated because of the intense pigmentation hypotension asthenia and intermittent episodes of *hypoglycemia In other patients disturbances in the secondary sexual char*acteristics have suggested hypogonadism as a factor The finding of osteoporosis with secondary calcification of the subcutaneous tissue has even been attributed to hyperparathyroidism Multiple involvement of the endocrines probably is merely secondary to the diffuse disease process and is nonspecific

More recently primary vascular phenomena have been regarded as the responsible factor in some patients [8, 9] The frequency of Raynaud s disease as a precursor and the frequent sclerodermatous involvement of the blood vessels have supported this concept There is little doubt that vascular involvement and angiospastic ischemia may exaggerate the pathologic process or even determine its site of predilection In one patient whom we observed the sclerodermatous changes were limited to one extremity The patient kept this arm elevated above her head frequently during the day while working as a wool comber Vascular studies performed subsequently demonstrated a precipitous fall in pulse pressure and blood flow when this extremity was elevated above her head

That emotional factors may play a part in eliciting angiospastic phenomena is indicated by the fact that clinical exacerbation sometimes follows an emotional crisis [5] Episodes of Raynaud s disease are often directly precipitated by such psychologic stimuli

Pathology The disease is not limited to the skin but also produces diffuse stiffening and rigid induration of other connective tissues of the body Histologically the disease process involves the collagen tissue primarily There is first a mild swelling of the intercellular collagenous substance at this time collections of small round cells may be scattered throughout the involved tissue In the later stages the collagen tissue becomes characteristically thickened dense and acellular This dense fibrosis represents the typical pathologic change Similar findings may be seen in the media and adventitia of some of the smaller blood vessels with gradual decrease in the caliber of the lumen and even eventual occlusion Well defined arteritis has been found in the kidneys heart and lungs (Talbot Masugi cited by Klemperer Pollack and Baehr[9]) In the early subacute stage, the vascular lesion may show fibrinoid degeneration of the collagen resembling the lesion seen in lupus erythematosus

Fibrotic changes may occur in the tongue buccal mucosa esophagus and interalveolar septa of the lungs liver, spleen kidneys thyroid and heart Weiss and his associates[10] have focused attention upon the diffuse systemic involvement They have demonstrated that the myocardium is very frequently scarred with vascular connective tissue

Symptoms The onset of the disease is usually insidious with the symptoms merging almost imperceptibly with the preceding state of good health Patients rarely complain at first of skin changes but rather of mild stiffening of the extremities and jaws Arthralgias morning stiffness and muscle weakness usually predominate In at least 50 per cent of the patients signs of vasomotor instability and Raynaud s disease are present Attacks characterized by cold and cyanotic extremities may recur for years before skin changes attributable to scleroderma become apparent Less frequently an early presenting complaint may refer to the gastrointestinal tract the lungs or the myocardium Dysphagia due to progressive fibrosis of the esophageal wall pulmonary embarrassment due to fibrosis of the lung or signs of myocardial failure may mask the rest of the clinical picture Infrequently the onset of the disease is acute and explosive with fever nonpitting generalized edema and very prominent joint pains suggesting the diagnosis of rheumatoid arthritis

The skin changes are usually not generalized at first the earliest detectable alterations occurring in the upper extremities and the face These lesions are usually symmetrical but focal vascular changes may induce more extensive findings in only one extremity Although the historical descriptions of the disease emphasized that the earliest skin changes consisted of a prominent nonpitting edema [31] most patients are not seen in this stage The earliest signs are rather a firm nonpitting induration of the skin and subcutaneous tissue (hard tight skin) These are most marked peripherally and gradually encroach upon the proximal ends of the extremities A characteristic early sign of scleroderma is a firm induration of the cheek so that downward retraction of the skin of the malar eminence fails to depress the lower eyelid It then spreads to the forehead nose lips extremities and torso In the affected areas, normal skin markings are replaced by a smooth ivory appear

ance Usually local hair growth disappears and in some instances even skin sweating ceases Typically, increased bronze pigmentation is often noted in involved areas This pigmentation may be diffuse or, more likely patchy with the dark areas interspersed with sharply demarcated areas of vitiligo thereby producing what has been termed the *piebald* appearance At this stage the vasomotor symptoms are usually pronounced with frequent episodes of cyanosis tingling and hyperesthesia in the finger tips

As the disease progresses the skin becomes increasingly tense and atrophic face wrinkles disappear and a typical masklike expression ensues The eyelids are retracted the thin lips are pressed together with multiple radial furrows the nose appears sharp and pinched and the chin and lips are puckered The fingers become semiflexed immobile and useless with the overlying skin inelastic pallid and incompressible—the typical claw hand The terminal phalanges appear boardlike with atrophy and sometimes ulcerations at their distal ends Frequently calcium plaques are deposited around the phalangeal joints and diffuse calcinosis may in some *instances become extensive Gradually movement of the neck swallowing* speech and blinking are all increasingly impaired The chest wall is immobilized by the restricting tense leathery skin respirations are increasingly labored and myocardial failure may supervene In the terminal stages the patients are cachectic hopelessly rigid and immobile and converted to veritable mummies

Albuminuria mild anemia elevated E S R and mild hyperglobulinemia may all be present Fluoroscopic examination of the esophagus during the swallowing of a barium mixture may fail to show any peristalsis X ray examination of the gastrointestinal tract frequently reveals a characteristic nipplelike constriction of the distal end of the esophagus with marked dilatation above Occasionally chest X rays demonstrate a perihilar diffuse fibrosis which fans out peripherally into the lung fields [32] The bones of the involved area may show considerable osteoporosis X rays of the deformed hands sometime reveal extreme degrees of atrophy of the peripheral ends of the phalangeal bones with coarse depositions of calcium in the periarticular tissues (tophi) The electrocardiographic findings depend upon the degree of myocardial involvement but consist usually of nonspecific T wave changes with occasional auricular tachycardias or conduction disturbances

Prognosis The natural course of diffuse scleroderma is usually one of progressive involvement of the skin and internal organs with a fatal termination Recurrent exacerbations and remissions are the rule In some patients the disease has persisted for 15 to 20 years Very often the premonitory symptoms of stiffness arthralgias and Raynaud s disease may precede the first objective evidence of scleroderma by four to five years The patients usually succumb to malnutrition cachexia secondary infection or cardiopulmonary failure

Dermatomyositis

Definition Dermatomyositis is a chronic nonsuppurative inflammation of the skin and muscles characterized by a vague insidious onset of progres-

sive weakness dermatitis and muscle inflammation The disease was first described in 1886 by Wagner[33]

Incidence and Etiology Although the disease may occur at any age, it usually develops between the ages of 10 and 50 There is no sexual predominance The cause remains obscure

Pathology The characteristic pathologic feature is hemorrhage and edema of striated muscle and of the adjacent interstitial collagen tissues which are often infiltrated with inflammatory cells The walls of the blood vessels may be thickened by extensive edema cellular infiltration and fibrinoid degeneration of the collagen fibers The muscle bundles reveal consistent proliferative and degenerative changes with giant cell formations and increase in number of the sarcolemma nuclei In addition to edema the muscle fibers show loss of striations fragmentation atrophy necrosis and sometimes hyaline granular fibrinous or vacuolar degeneration The skin undergoes atrophy of the epidermis and usually reveals perivascular infiltration of the corium with lymphocytes and plasma cells The histologic changes in the muscle are not pathognomonic for dermatomyositis for they may also be found in rheumatoid arthritis thyrotoxicosis pneumonia, scleroderma and polyarteritis

Symptoms The disease usually begins with low grade fever weakness lassitude and malaise Sooner or later however the predominating symptoms refer to the musculature Although any muscle or combination of muscles may be affected the proximal muscle groups are usually more involved than the distal[34] Typically the fingers may remain uninvolved whereas the shoulder girdle may show signs of extensive disease The course progresses from mild morning stiffness to increasing weakness and muscular tenderness Eventually the affected muscles may lose all semblance of function and the patient lies motionless in bed In almost every instance the muscles are painful and exquisitely tender to pressure On palpation they may seem indurated and firm or soft and flabby In some cases the disease is limited to one group of muscles or even to one extremity in other instances various groups of muscles seem to manifest involvement in waves the symptoms in one group subsiding completely as another group becomes progressively involved The cervical dorsal abdominal and trunk muscles often show evidence of disease Occasionally the muscles of the pharynx larynx tongue and soft palate are involved so that disturbances in swallowing and speech result Ultimately the diaphragm and other respiratory muscles may suffer serious damage producing asphyxia and frequent aspirations When the heart muscle is affected tachycardias abnormal electrocardiographic changes and even circulatory failure complicate the clinical picture[35]

Very frequently the skin and subcutaneous tissues overlying the diseased muscle are indurated and edematous This swelling commonly affects the face and may produce a tense edema of the eyelids Any portion of the skin of the body may present a wide variety of lesions such as urticarial blebs nonspecific eczematoid reactions generalized pruritus and maculopapular

rash or erythema multiforme Localized or generalized hyperhidrosis, petechiae multiple and irregular areas of brown pigmentation telangiectases and even sclerodermalike changes in the skin are not unusual in dermatomyositis The latter changes have sometimes been so pronounced as to suggest to some observers that scleroderma and dermatomyositis represent different stages of the same disease process

Involvement of the nervous system combined with the primary manifestations of muscle swelling edema and exanthema of the skin often completes the clinical picture Symptoms of hyperesthesia and numbness of the hands and feet lancinating pains and foot drop may then be present Whereas deep tendon reflexes are usually depressed or absent when the muscles are involved supratentorial changes may cause increased tendon reflexes and other pyramidal tract signs In the very rare form of the disease called *neurodermatomyositis* the neurologic symptoms and signs may be particularly conspicuous

Splenomegaly hepatomegaly and lymphadenopathy are unusual

The laboratory findings are not of diagnostic or prognostic help Anemia leukopenia or leukocytosis are rarely prominent eosinophilia has been described in about 25 per cent of the patients The E S R is markedly elevated especially during an acute exacerbation Mild to moderate albuminuria and microscopic hematuria occur in about one third of the patients although nephropathy is rarely a predominant feature The albumin globulin ratio is usually reversed with a significant hyperglobulinemia Disturbance of the creatine metabolism characterized by a persistent creatinuria and a decreased tolerance to ingested creatine is usually present This feature probably reflects the diffuse inflammation of the musculature rather than any specific alteration Muscle biopsies are often made to confirm the diagnosis even though a diagnosis based solely on pathologic grounds may be questioned because of the lack of specificity of the pathologic findings

Trichinosis can produce a similar picture of muscle involvement fever swelling of the eyes and even cardiac involvement The muscular involvement in trichinosis is more acute cutaneous manifestations are much less marked there is usually an antecedent history of gastrointestinal disturbances and facial edema eosinophilia is conspicuous and the calcified larvae may be readily demonstrated in a muscle biopsy

Prognosis Untreated the disease is usually progressive and most observers report a fatality rate of 50 to 60 per cent The course however is extremely variable and may persist from weeks to 10 or 12 years As with other collagen diseases the clinical picture is often characterized by recurrent exacerbations and remissions not infrequently a long period of quiescence will be followed by a sudden flare up involving a new group of muscles This unpredictable irregular course complicates the evaluation of any therapeutic measure Death is usually precipitated by increasing involvement of the respiratory muscles progressive cardiac involvement or simply a gradual overwhelming weakness paralysis and debility

Hormonal Therapy

Cortisone and corticotropin represent the only effective agents for the arrest or symptomatic control of the collagen diseases. Although these hormones have been used in each of these diseases the largest experience has been accumulated in acute disseminated lupus erythematosus.[11 36 37] These comments will therefore emphasize the effects of cortisone and corticotropin in the latter disease.

When used in adequate dosage the hormones are dramatically effective in controlling the clinical manifestations. Usually the temperature falls to normal within 48 hours, tachycardia and gallop rhythm subside after 3 to 4 days and the joint pains are completely ameliorated within 1 week. Clinical and roentgenographic evidence of pleuropericardial involvement gradually disappears after 7 to 14 days of hormone administration. The skin lesions fade more slowly. Within one week the violescent erythematous hue disappears, the lesions then gradually undergo brownish pigmentation and finally fade during subsequent months. Resolution of the hemorrhages and exudates in the eyegrounds occurs over a more prolonged period of therapy.

In our experience cortisone and corticotropin have been equally effective in the control of disseminated lupus erythematosus although in terms of dosage corticotropin is about twice as potent. The ease with which cortisone may be administered orally has made it the agent of choice for most patients. The usual starting dosages are 150 to 250 mg of cortisone per day administered in four equal doses by mouth or 100 units of corticotropin divided into four intramuscular injections. Both oral cortisone and parenteral corticotropin will usually produce their first effects within 18 hours. For critically ill patients daily dosages as high as 500 mg of cortisone and 300 units of corticotropin in divided doses every two hours have been required. Occasionally when a patient is desperately ill and an immediate response may be lifesaving corticotropin can be administered intravenously in a glucose infusion. In this form each unit is approximately ten times as effective as when given intramuscularly. Accordingly 25 to 50 units administered daily in a slow infusion will often produce a prompt clinical response.

A poor symptomatic response despite adequate dosage usually indicates the presence of an intercurrent infection. Accordingly all patients particularly in the acute stage should be treated simultaneously with adequate antibiotic therapy. These hormonal agents have an adverse effect upon some infections and this emphasizes the importance of simultaneous antibiotic therapy during the first week or longer.

After the clinical manifestations of the disease have been under complete control for 10 days to 2 weeks the dosage may be reduced in stepwise fashion until the minimum daily amount required for the maintenance of clinical remission is determined. Serious relapses of disseminated lupus erythematosus have followed abrupt discontinuation of hormonal therapy. This is much less likely to occur when the dose is slowly reduced during a period of several weeks or months. It is our custom to reduce the dosage at intervals of not

less than three or four days by no more than 5 or 10 mg of cortisone per day Such fine adjustment of dosage will be facilitated by the use of 5 mg tablets of hydrocortisone

With continued therapy there is usually a progressive improvement in strength and general well being The patients often develop voracious appetites gain weight and fill out their depleted tissues In some patients it is ultimately possible to di continue therapy for considerable periods of time without immediate recurrence In about two-thirds of the patients however maintenance therapy must be continued indefinitely Subjects have been sustained relatively symptom free for two to three years with daily dosages of corti one of 25 to 75 mg orally or with parenteral use of corticotropin in doses varying from 5 to 50 units During periods of remission it may even be possible to administer the hormone less frequently At such times a single 25 mg cortisone tablet may provide freedom from symptoms for 10 to 12 hours, after which another dose may be necessary In most instances it is necessary to administer the daily maintenance amount of cortisone in two to three divided doses

The recent development of a prolonged acting purified corticotropin gel has enhanced the value of this particular hormone for maintenance therapy A single injection of the gel daily may afford a beneficial effect for the entire 24 hour period In one patient a daily 5-unit injection of corticotropin has maintained a clinical remission for 24 months yet cessation of this tiny dose is usually followed in 48 to 72 hours by fever joint pains or pleurisy Frequently a maintenance dosage of cortisone or corticotropin must be chosen which will provide maximal freedom from troublesome symptoms compatible with minimal disturbance from undesired effects of the hormone

Occasionally a patient will develop an acute exacerbation despite careful maintenance and will require readmission to the hospital for more intensive therapy Despite prolonged and intermittent therapy the clinical manifestations repeatedly re pond to renewed cortisone or corticotropin therapy Patients rarely develop increasing refractoriness to these hormonal agents even when maintenance therapy has been continued for periods up to three years

During the course of cortisone or corticotropin therapy considerable improvement occurs in many of the abnormal laboratory findings characteristic of disseminated lupus erythematosus The anemia usually improves In patients who exhibit laboratory evidence of an autohemolysin and a hemolytic anemia these abnormal findings similarly disappear under hormonal therapy The leukopenia usually improves to some extent but in most of the patients it persists in some degree during remissions of the disease The thrombocytopenia likewise reveals considerable improvement Even when the thrombocytopenia has been so marked as to mimic the picture of idiopathic thrombocytopenic purpura a significant increase in the number of circulating platelets may occur after adequate hormonal therapy The E S R returns to normal in less than one half of the subjects

Serial electrophoretic patterns during the course of cortisone therapy

reveal a slow increase in the serum albumin concentration and a reciprocal reduction in the gamma globulin concentration but these changes may only occur after several months of successful treatment The nephrotic picture may then improve if it is the result of hypoproteinemia and is not associated with irreversible renal damage The increase in the alpha 2 globulin fraction which Reiner[15] described as a characteristic finding in lupus erythematosus persists like the leukopenia the L E cells and the abnormal E S R even when a clinical remission has been induced by cortisone or corticotropin

The serum hexosamine which reflects the degree of alteration in the mucoprotein of the ground substance and is conspicuously increased in acute disseminated lupus erythematosus falls to normal levels as the clinical manifestations are suppressed [11] Indeed alterations in this hexosamine concentration seem to parallel the clinical activity of the underlying disease

Renal damage which may have occurred during exacerbations of the disease appears to be largely irreversible Albuminuria, microscopic hematuria and cylindruria for the most part persist During the acute phase of the disease a mild prerenal azotemia may be attributable to dehydration fever and tissue catabolism, and plasma urea concentrations will revert toward normal after some symptomatic improvement has been accomplished But if the azotemia reflects underlying renal involvement cortisone or corticotropin will not reverse this finding even in patients in whom a satisfactory clinical response is induced Azotemia persists or may even increase in intensity, and the patients ultimately succumb to uremia

Although others have reported the disappearance of L E cells during clinical remission this characteristic phenomenon has persisted in almost all of the patients we have treated over prolonged periods In several subjects the cells have been reduced in number and occasionally they have even disappeared temporarily, but this pathognomonic abnormality can be found during cortisone-induced remissions if blood and bone marrow are repeatedly examined

The pathologic findings in patients coming to postmortem examination after prolonged cortisone or corticotropin therapy have been similar to those observed in the precortisone era and the pathognomonic hematoxylin bodies have been as conspicuous

Undesired Effects of Hormonal Therapy

The type of complication noted early in cortisone or corticotropin therapy tends to differ from that observed after prolonged treatment Nevertheless a firm line of demarcation cannot be drawn between these two types of toxic' effects An untoward effect which is usually conspicuous only in the first days of therapy may persist as treatment is prolonged and occasionally may even appear for the first time after a considerable period of therapy

The most prominent and frequent complication encountered in the early stages of therapy with cortisone or corticotropin relates to effects similar to those produced by desoxycorticosterone The majority of patients retain considerable quantities of salt and may develop edema hypertension or even

congestive heart failure To a considerable extent these sequelae of salt retention may be avoided by a carefully restricted sodium free diet Furthermore some have claimed that large doses of potassium chloride will reduce the amount of sodium retained by the kidneys Even on a salt-free diet (containing less than 200 mg of sodium a day) cortisone and corticotropin will evoke a transfer of endogenous sodium chloride and water into the fluid phase of the extracellular compartment [35] The amounts involved in such shifts approximate 1 5 to 2 5 liters but without coincident exogenous salt retention this is not usually sufficient per se to produce edema and congestive heart failure Furthermore this redistribution of body water into the extracellular compartment is transient producing maximal effects after seven to nine days of therapy and disappearing subsequently despite continued hormone administration

It should be emphasized however that the underlying cardiovascular disability in patients with disseminated lupus erythematosus sensitizes these subjects to the ill effects of expanded extracellular volumes whether these expansions derive from endogenous or exogenous sources The development of congestive heart failure during early stages of cortisone or corticotropin therapy is often preceded by an abrupt increase in body weight or by the sudden appearance of hypertension Circulatory failure may manifest itself as an acute attack of pulmonary edema or acute hepatic engorgement Usually it can be effectively combated with Mercuhydrin digitalis bloodless phlebotomy sedation and oxygen without discontinuing hormonal therapy In several patients these measures have induced a 10 pound diuresis in 18 hours and a remarkable recovery

The negative potassium balance associated with cortisone or corticotropin therapy often produces hypokalemia and hypochloremic alkalosis The alkalosis is usually mild and of little clinical significance The diuresis of chloride potassium and water however when Mercuhydrin or other diuretic agents are administered to control edema will markedly exaggerate this electrolytic disturbance In several patients in whom repeated mercurials were necessary we have observed plasma potassium concentrations as low as 2 0 mEq per liter chloride concentrations reduced to 70 mEq per liter and bicarbonate concentrations as high as 40 to 45 mEq per liter When such severe degrees of alkalosis occur they may be corrected by the judicious administration of potassium and ammonium chloride A salt free diet decreases the urinary potassium loss By this means and by eliminating the necessity for frequent Mercuhydrin injections such a diet reduces the frequency and severity of the complicating alkalosis

The tendency to retain salt becomes less marked as hormonal therapy is continued In fact a distinct salt diuresis may occur after 10 to 14 days of hormone administration Consequently the complications attributable to salt retention become much less troublesome as therapy is prolonged This may reflect the improved cardiac function under the influence of hormonal therapy and the progressive reduction in the hormone dosage as the manifestations of the disease are controlled Nevertheless, if patients ingest large

quantities of salt, edema and congestive heart failure may ensue at any stage of therapy Accordingly all patients treated with large daily doses of either cortisone or corticotropin should be maintained on a salt free diet with the intermittent administration of 4 to 8 Gm of potassium chloride per day Until the hormonal therapy can be reduced to low maintenance dosage the daily diet should not contain more than 200 mg of sodium

Some degree of hypertension is detected in the vast majority of the patients during the first two weeks of therapy This elevation of blood pressure may be related in part to the coincident salt retention yet not infrequently significant blood pressure rises have been noted in the absence of any detectable weight gain Whatever its cause the hypertension is not usually troublesome and tends to disappear with continued hormone administration Certainly any elevation of blood pressure does not contraindicate the inception or continuation of hormonal treatment Its persistence or recurrence after prolonged therapy in the absence of obvious salt retention should suggest the presence of underlying renal involvement

In patients with disseminated lupus erythematosus convulsive seizures are an infrequent but sometimes disastrous complication of hormonal therapy These seizures take the form of generalized epileptiform clonic and tonic convulsions and usually develop in the first 7 to 14 days of treatment One 12 year old girl who had shown a remarkable symptomatic response after eight days of corticotropin therapy suddenly developed status epilepticus which led to coma and death In 3 other subjects however one or two generalized seizures occurred and were inhibited thereafter with anticonvulsant drugs so that cortisone or corticotropin could be continued Epileptiform convulsions were observed during periods of exacerbation of lupus erythematosus long before the use of hormonal therapy It had been originally hoped that frequent electroencephalograms (EEG s) might give prior warning of the development of convulsive seizures However the EEG s are so often abnormal during the acute stage of disseminated lupus erythematosus that they offer little help in predicting the onset of these seizures In 2 subjects severe intractable headaches preceded the convulsive episodes by 24 to 48 hours

A number of patients undergo striking mental changes during the first month of adrenal hormone therapy At first they show general improvement in mood coincident with the disappearance of the weakness toxicity and distressing joint pains Some become very cheerful extremely alert and even euphoric Subsequently the alteration in mood may be characterized by severe psychotic depression Episodes of severe depression alternated in one patient with periods of mental elation and manic outbursts A second manifested pronounced apathy visual and auditory hallucinations, and expressions of bitter resentment toward the medical staff In some patients depressions have centered about threats of self destruction and suicides have been reported Although no instance of suicide has occurred in our series on several occasions this danger has warranted cessation of therapy For the most part however, it has been possible to continue hormonal

therapy, and these personality changes have subsided as the dosage was gradually reduced Occasionally less blatant personality changes persist even on relatively low maintenance dosages such as slight irritability, a subtle change from a generous, forward personality to one that is bitter resentful and suspicious In some patients insomnia may be troublesome while the hormone is being taken

Whether these personality changes represent exaggerations of preexisting traits has not been proved It has been reported that large doses of potassium chloride inhibit the convulsive seizures as well as the gross mental aberrations This report does not conform to our experience It should be emphasized that the presence of toxic psychoses and organic mental syndromes as *manifestations of the primary disease process does not increase the likelihood* of superimposed psychotic reactions after cortisone or corticotropin administration In fact, 3 patients have shown complete resolution of such manifestations after one to two weeks of hormonal therapy

Frank diabetes has been an extremely infrequent complication of therapy in our experience Although transient glycosuria and hyperglycemia were noted in several patients persistent and massive glycosuria appeared in but 2 subjects In both this manifestation developed on relatively high dosage levels and was associated with marked urinary nitrogen loss Considerable amounts of insulin are necessary to control steroid diabetes but the impairment in carbohydrate tolerance usually disappears completely as the dosage of the administered hormone is progressively reduced In both subjects who displayed troublesome diabetes a strong positive family history was elicited It seems likely therefore that this complication will appear in those patients who are potential diabetics

Electrocardiographic changes including inverted T waves prolonged Q T intervals and sinus bradycardia occurred in several patients while under therapy Two subjects showed a complete auriculoventricular dissociation with a slow idioventricular rhythm Whether these changes are secondary to the electrolytic disturbances or to a direct effect upon the myocardium is not known In any event these electrocardiographic changes are usually transient and of little clinical import In no instance have they necessitated discontinuation of therapy

One of the most vexing difficulties encountered during sustained therapy with these hormones relates to their tendency to obscure the usual clinical signs of inflammation Some patients have developed a fulminating pneumonia or bacteremia while on therapy without conspicuous febrile reactions or marked toxicity One 26 year old girl succumbed to an overwhelming fungus infection of the lung without overt pulmonary signs Large gluteal abscesses secondary to parenteral therapy have developed with only meager evidence of local tenderness or warmth Perforated peptic ulcers without the typical signs of peritonitis have been reported Apart from the alleged influence of these agents in disseminating bacterial and fungus infections the detection of an intercurrent infectious process may pose a difficult problem Accordingly each patient on intensive hormonal therapy must be carefully

followed by frequent clinical and laboratory examinations Furthermore adjunctive antibiotic therapy should be administered whenever feasible to reduce the frequency of these intercurrent infections

As therapy is prolonged the stigmata of Cushing's syndrome become progressively conspicuous Their onset depends more upon the length of therapy than upon the specific dosage level With prolonged treatment increased skin pigmentation moon facies and buffalo hump become evident in most cases Many patients complain that new depots of fat have appeared on their shoulders and backs Hirsutism abdominal striae and aneform eruptions are often troublesome Occasionally when intensive therapy is maintained for long intervals this chronic form of "toxicity" is punctuated by an acute psychosis sudden congestive heart failure or other untoward effect more characteristic of the early stages of therapy Severe back pain developed in one subject after six months of hormone administration and subsequent X ray examinations revealed severe osteoporosis and lumbar collapse For the most part however clinical manifestations of negative calcium and nitrogen balance have not been prominent Consistent and marked elevations of the plasma cholesterol level have been recorded in several subjects Although it has been suggested that such a sustained lipemia may accelerate the premature development of atherosclerosis[39] evidence directly implicating this potential danger is not convincing

The prolonged use of either cortisone or corticotropin apart from its beneficial effect upon the underlying disease usually evokes a characteristic symptom complex with at least some of the features of hyperadrenocorticism The clinical picture may then include some of the persistent signs of the primary disease process and at least some undesired hormonal effects The attending physician must then balance the beneficial effects of the therapy in a fatal illness against the cosmetic implications of a symptom complex similar to Cushing s syndrome It should be emphasized that no matter how distressing the latter complications may be complete subsidence of the untoward effects of hormonal therapy follows soon after cessation of therapy or reduction of the dosage to minimal maintenance levels The importance of gradually reducing the dosage of cortisone or corticotropin, particularly in disseminated lupus erythematosus, has already been noted

Response to Therapy

Disseminated Lupus Erythematosus

Disseminated lupus erythematosus may be classified on the basis of the most conspicuous clinical manifestations into five or six relatively distinct clinical patterns each of which responds in a somewhat different manner to treatment Although this differentiation should not suggest any fundamental difference in the underlying disease it serves a practical purpose because each of these varied forms presents characteristic problems and responds fairly typically to prolonged hormonal therapy arthritic hematologic cerebral, cutaneous, and cardiorenal

Arthritic When the joint symptoms provide the sole manifestation of disseminated lupus erythematosus it is often possible to maintain the patients almost symptom free on a relatively low maintenance dose In those subjects in whom the symptoms attributable to polyserositis are particularly prominent the ready response to cortisone and corticotropin is also often gratifying We have not observed a single instance in which this form of the disease has not completely responded to adequate therapy On the other hand the development of hyperadrenocorticism may demand such a rigid reduction in dosage that complete control of the symptoms does not prove feasible [40]

Hematologic This form of the disease likewise usually proves susceptible to adrenocortical therapy Severe symptomatic hemolytic anemia accompanied by a positive Coombs test and active autohemolysins has responded to therapy with the subsequent disappearance of these abnormal hematologic findings Severe thrombocytopenia may disappear after two weeks of hormone administration

Cerebral Recurrent convulsions and mental syndromes which may occur as part of the illness are of unusual interest because similar complications may be induced by hormonal therapy Despite this fact adequate hormonal therapy usually suppresses these clinical phenomena when they are caused by the disease itself There is at present no evidence to suggest that these subjects are more likely to develop psychiatric complications from therapy Occasionally such patients are treated inadequately because the convulsive or psychiatric manifestations are mistakenly attributed to the hormones Under these circumstances more intensive therapy may produce a remission

Cutaneous The occurrence of the characteristic erythematous macular lesions as a sole manifestation of disseminated lupus erythematosus without some evidences of systemic illness is extremely uncommon When the skin lesions are particularly conspicuous however adequate therapy induces a favorable but slow response Usually considerable pigmentation remains in those areas which were maximally involved

Cardiorenal This feature of disseminated lupus erythematosus is resistant to hormonal therapy The myocardial vascular injury increases the therapeutic hazard It is sometimes extremely difficult to determine whether gallop rhythm pulmonary rales and sudden hepatic engorgement are the result of a pleuropericarditis or a toxic myocardial effect of the disease process or simply hormone induced salt retention and congestive heart failure Occasionally the determination of the circulation time and venous pressure may define the factor most responsible Usually however a combination of both the disease process and cortisone toxicity underlies the development of these findings the former predisposing the subject to the effects of salt retention For the most part therefore episodes of congestive failure should be treated actively with digitalis Mercuhydrin and low salt diet without discontinuing hormone administration Indeed insofar as primary myocardial involvement obtains an increase in hormone dosage sometimes has a favorable effect upon the circulatory failure

The manifestations of severe renal damage are not altered by cortisone or corticotropin. Of 5 patients with such findings, 4 have succumbed to the sequelae of renal insufficiency despite moderately good control of the other clinical manifestations. In part this progression reflects the widespread vascular involvement of the renal parenchyma prior to the onset of therapy. In addition, however, the occlusive vascular process may continue unabated after institution of adequate therapy, despite the suppression of all other clinical manifestations of the disease. The presence of persistent edema or hypertension after prolonged cortisone or corticotropin therapy should therefore suggest that considerable renal impairment may exist. Too often these findings are mistakenly attributed to hormone toxicity.

The renal form of the disease is further complicated by electrolyte abnormalities which may range from a typical hypopotassemic hypochloremic alkalosis caused by the hormonal therapy to severe renal acidosis or may include any combination of the two. In the presence of renal insufficiency the use of potassium chloride for the correction of hypochloremic alkalosis is attended by considerable risk. When edema supervenes in these patients Mercuhydrin is of little value. In a limited number of subjects the edema and hypochloremic alkalosis may be partially corrected by employing the cation exchange resins. However, meticulous care must be taken to avoid severe acidosis from this form of therapy. When uremia and renal acidosis are conspicuous, the measures used for the more common forms of renal insufficiency should also be employed.

These hormonal agents are able to suppress many of the clinical manifestations of disseminated lupus erythematosus and they prolong life in a considerable number of patients. The long term use of cortisone and corticotropin is feasible if careful and frequent clinical and laboratory observations are made. During the past three years more than 20 patients critically ill with acute disseminated lupus erythematosus have been admitted for hormonal therapy. Of this number 4 have succumbed during this time to uremia, 1 to corticotropin induced status epilepticus and 1 to a virulent fungus infection, but 13 of these patients have been maintained in a state of at least partial remission by relatively constant hormonal therapy for periods varying from one to three years. The persistence of the L E cell, of leukopenia, and in most instances of an accelerated E S R, the pathognomonic microscopic findings at postmortem after prolonged therapy, the tendency to exacerbation when hormonal therapy is discontinued, and the progression of renal abnormalities despite adequate control of the other clinical manifestations—all demonstrate that these hormones act only as suppressive agents. Although they may inhibit local tissue reaction to the offending etiologic factor [41] the unknown etiologic factor and the basic disease process remain uncontrolled.

Polyarteritis

The conclusions drawn from the results of cortisone and corticotropin therapy in disseminated lupus erythematosus may be applied to poly

arteritis These agents effect a considerable improvement in such manifestations of the disease as fever asthma eosinophilia joint and muscle pains, and a multitude of allergic skin reactions In the presumably allergic form of the disease characterized by eosinophilia and transient and migratory pulmonary infiltrations (Loeffler s syndrome), the response may be striking The characteristic roentgenographic shadows may disappear in 48 to 72 hours As with disseminated lupus erythematosus however therapy must usually be continued on a semipermanent basis to maintain the state of remission

On the other hand when extensive vascular involvement of the heart and kidneys and hypertension predominate the effects of permanent vascular damage upon the parenchyma of these vital organs often lead to death despite the suppression of other clinical manifestations Insofar as the polyneuritic signs reflect primary occlusive vascular disease these findings are similarly resistant to hormonal therapy Any underlying cardiac and renal disease as in disseminated lupus erythematosus complicates the use of these hormonal agents and depresses the ultimate prognosis

Diffuse Scleroderma

The therapeutic response in patients with diffuse scleroderma is conditioned by the proportion of early tissue alteration in comparison with irreversible dense sclerosis and vascular obliteration In several patients in whom the disease was quite recent in onset and relatively acute considerable improvement occurred both in the induration of the skin and the Raynaud s disea e As with the other collagen diseases the improvement persisted only as long as therapy was continued [4] In those patients in whom prolonged irreversible tissue sclerosis and fibrosis predominated the therapeutic results were less impressive The therapy of scleroderma also poses the problem of prolonged administration—often at consistently high dosage levels Even under these circumstances the response to therapy is usually negligible because of the irreversible nature of the tissue alterations

Dermatomyositis

The effectiveness of cortisone and corticotropin in dermatomyositis is still to be determined The therapeutic result will depend in each instance upon the proportion of the irreversible to reversible pathology [43] We have observed several patients in whom a remarkable response has followed the inception of adrenal hormone therapy with rapid disappearance of muscle weakness and inflammation In two of these patients the remission has persisted despite the di continuance of therapy Other patients however have not responded to cortisone or corticotropin therapy Patients with this disease should receive the benefit of hormonal treatment as soon as possible for symptomatic improvement can be achieved in early cases The ultimate results must await longer follow up observations

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6

Asthma and Rhinitis

Bram Rose

In the five years that have passed since cortisone and corticotropin were first used as therapeutic aids in the control of allergic disease in man [1–5] considerable literature on the subject has been published Sufficient time has now elapsed for the effects of long term treatment to be observed and for these agents to be evaluated with a greater degree of accuracy in the light of experience In this chapter an attempt will be made to review the existing literature even though several earlier reviews are available [6–9]

It may be said at the outset that the advent of both cortisone and corticotropin marked a notable advance in the treatment of hypersensitivity and that when properly used in man, they are the most valuable therapeutic agents at present available Initial reports of the dramatic effects of these hormones upon asthma have repeatedly been confirmed by numerous observers These consist of rapid disappearance of such signs and symptoms as cough dyspnea and sputum In the majority of patients appetite increases and there is a gain in weight Nevertheless it must be emphasized that neither hormone represents a cure and as is well known the effects are temporary Both are capable of inducing marked alterations in metabolism and are potentially dangerous if used without care With the increasing use of cortisone and corticotropin both the clinician and the pathologist have been forced to become familiar with their properties One sees fewer and fewer asthmatics who have not had at least a trial of cortisone or corticotropin Yet it is the opinion of almost all observers that no patient with either asthma or rhinitis or both should receive adrenocortical therapy to the exclusion of other forms of therapy or without a complete investigation and an adequate trial of conventional methods

Comparison of the Effects of Cortisone and Corticotropin

The chief advantages of cortisone are that it can be administered orally and is independent of the state of the adrenal gland itself Thus it is useful

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in Addison's disease whereas corticotropin is ineffective in this condition Either cortisone or corticotropin may be used in asthma and allied conditions There is as yet no clear cut difference in effectiveness between the two preparations when each is administered in adequate dosage

Corticotropin either in the lyophilized form or the newer long acting preparations is active only by parenteral routes such as the intravenous, subcutaneous or intramuscular Since these preparations may contain foreign protein they may at times produce reactions of the anaphylactic type [9–14]

The effects of cortisone and corticotropin are numerous and will not be considered in detail in this chapter with the exception of those directly related to the subject It may be of interest to note however that of the many metabolic changes such as alterations in protein carbohydrate and electrolyte metabolism no essential pattern distinguishes the allergic manifestation from other forms of disease, with the possible exception of alterations in the urinary excretion of histamine In the initial work of Rose et al [15] in which protein balance studies and blood and urine electrolyte as well as urine histidine and histamine determinations were made a negative nitrogen balance and a tendency toward sodium and chloride retention and potassium excretion were observed In all cases histidine excretion was increased [16] and this has been observed especially by Holbrook et al [17] Although Grob[18] was unable to show much of an increase in the urine histamine Rose et al [19] have noted rather phenomenal quantities of a histamine like substance in the urine of patients with various forms of allergy However there was neither consistency in the quantities excreted nor relation to cortisone or corticotropin therapy

Of perhaps greater interest is the excretion of the glucocorticoids substances similar to compound E and measured biologically in the urine [1] Venning Johnson and Rose [1] have noted that the output of this steroid is generally low in older patients with asthma of the intrinsic variety and may be stimulated to within normal limits by the administration of corticotropin In younger patients with asthma of the extrinsic variety the values are usually within normal limits and corticotropin is capable of stimulating a considerable release of the compound by the adrenal cortex The measurement of the 17 ketosteroids though of interest is of little value in determining adrenocortical function in asthma or other allergic phenomena

It is difficult to say whether allergy occurs because of a hypofunctioning adrenal which is incapable of meeting the demands made upon it or whether the hypersensitive state is unable as such to stimulate the pituitary adrenal mechanism Some evidence in favor of the latter theory has been presented by Rose

It is of interest that many changes directly concerned with hypersensitivity are markedly affected by cortisone or corticotropin Examples are the depression of eosinophils lymphocytes and erythrocyte sedimentation rate (E S R) the suppression of the inflammatory response in the skin to bacterial vaccines [3–25] the increase in tolerance of a patient to a specific antigen [6] and the reduction in lymphoid tissue That these examples do not

give the whole answer seems evident since a number of other phenomena associated with the immune response and with hypersensitivity in general do not appear to be affected For example certain types of antibody formation are suppressed [27, 28] whereas others are not altered [29, 30] The immediately reacting skin test remains unchanged during cortisone or corticotropin administration [26, 31–34]

Asthma

Selection of Patients for Treatment with Cortisone

In the early days of cortisone and corticotropin only patients with the *most intractable and long standing asthma were chosen for study in order* to provide incontestable proof of the efficacy of these compounds Since that time they have been given in virtually all types of asthma or rhinitis Such lack of selection is to be deprecated As is rightly pointed out (in particular by Kern[35] and Cooke et al [36]) not only does it lead to the unnecessary use of cortisone but it is a poor approach to the treatment of the allergic state It will be seen from the literature that as use of these compounds becomes more widespread *more and more patients appear to become dependent* upon them This cannot be regarded as habit or addiction since there would be no desire on the part of the patient to take either preparation were relief available by other means Sherman[37] states that the need for adequate surveys and skin testing of these patients is even greater today than before the advent of adrenocortical therapy Furthermore *a remission obtained by conventional forms of treatment such as elimination of foci of infection and allergens together with hyposensitization is always more satisfactory than the temporary state of remission induced by cortisone or corticotropin*

The choice of patient depends upon a number of factors Best results are obtained in the proved case of asthma in which the patient is free from any contraindications to the use of cortisone and has failed to respond to conventional forms of therapy It may be well to distinguish here between the two groups of asthmatic manifestations The first is so-called *extrinsic* or *allergic* asthma in which symptoms are caused primarily by the presence of external environmental factors as well as by an inherited tendency to develop allergy Infection although it may be a factor, is not usually the etiologic agent and the symptoms promptly subside once the offending allergen is no longer present Patients with extrinsic asthma usually do well with conventional forms of treatment such as injections of mixed grasses or ragweed or the molds depending upon the history and skin tests It must be admitted nevertheless that a considerable percentage of such persons develop rather severe asthma during the time of maximum pollen counts and become problems for the physician For this type of patient cortisone, in a sense provides the ideal treatment because the duration of treatment is short Symptoms subside once the pollen season has ended Thus Carryer et al [5] Friedlaender and Friedlaender [38] Stier et al [6] and Randolph and Rollins[39] have reported fair to excellent results in this form of pure asthma

The second and perhaps larger group of so-called *intrinsic* or *nonallergic* asthma presents a more difficult problem Here the symptoms appear in later life often following infection of the respiratory tract in the form of rhinitis and bronchitis in the fall of the year There is an associated cough with sputum production In many of these patients the infection becomes chronic and difficult to treat They often respond to eradication of the foci of infection as well as to antibiotic therapy Many of course fall into neither one category nor the other These are the *mixed cases* In view of the reported numbers of patients who have been treated with cortisone or corticotropin it is apparent that few such patients respond to conventional forms of therapy The majority appear to have been benefited enormously by the advent of cortisone [4 13 6 36–55] It is perhaps unfortunate that many of these require almost constant or repeated hormonal therapy Whether this is due to inadequate attempts at conventional treatment is difficult to say Regardless of these considerations it seems clear that when the patient has to make the choice the ability to continue work and the feeling of well being due to cortisone therapy are preferred to the semi invalidism associated with the chronic asthmatic state which resists other forms of therapy

General Management It is agreed by most observers that for the usual patient certain precautions are necessary before treatment is instituted and that close supervision during the period of treatment is essential These precautions should include care in taking the history and a physical examination supplemented by urinalysis chest X ray to eliminate the possibility of the presence of active pulmonary tuberculosis an electrocardiogram when indicated and appropriate blood sugar determinations

During treatment the patient should be placed on a low salt diet of 1 to 3 Gm daily and a potassium supplement should be given particularly if cortisone is given in large doses Either potassium chloride or potassium iodide in enteric coated capsules is suitable the dosage being 3 to 5 Gm per day The blood pressure should be checked frequently weight recorded and urine reexamined

The possibility of spreading an infection must always be borne in mind though there is some controversy regarding this point [56–58] Signs of inflammation or infection such as fever leukocytosis pain and swelling may be completely masked by cortisone in high dosage [59] Some infections may be spread [58 60] whereas others such as lobar pneumonia spread locally [61 6] but do not produce their typical systemic effects In any case death during corticotropin therapy has occurred as a result of the masking of the signs of infection and failure to recognize the presence of widespread bronchopneumonia [63] It would appear that it is safest in all cases to realize that infection may be enhanced

There seems little doubt that many low grade chronic upper or lower respiratory infections contributing to cough sputum and maintenance of symptoms vanish with cortisone therapy Since cortisone suppresses the toxic effects of infection this might be interpreted as an over all increase in the resistance of the patient Further most infective processes in man

respond better to antibiotic therapy in conjunction with cortisone than they do to either of these agents when given alone It is probably wisest therefore, to use a suitable antibiotic along with cortisone therapy whenever there is any question about the presence of infection [64] The remainder of the precautionary measures have to do with undesired effects and will be dealt with in the section Complications of Cortisone Therapy

Administration and Effective Dosage Schedules

To judge from the experience gained in treating large numbers of patients there appears to be no hard and fast rule regarding dosage each case being a law unto itself It is also obvious that the amount of cortisone required is related to the severity of the disease process rather than to age or body weight Thus as much as 2 000 mg a day of cortisone has been administered orally to patients with disseminated lupus erythematosus or pemphigus[65] and 500 to 600 mg daily to some with intractable asthma [63]

In an early report Glaser et al [66] expressed the view that larger doses were required for children than for adults In our experience the dose required for treatment of acute asthma is as high in children as in adults The average maintenance dose however may be somewhat lower for the child

Two types of preparation are available for the treatment of asthma and rhinitis The first is the suspension of cortisone acetate containing 25 mg of the active principle per cc which may be given intramuscularly or orally When administered intramuscularly it usually takes from 24 to 36 hours to exert an effect Similarly, on withdrawal the effect may last one to three days Using the parenteral route Carey et al [4] administered 300 mg on the first day and 200 mg daily for an additional nine days, or 200 mg on the first day followed by 100 mg daily for an additional seven days Minor variations in dosage such as 300 and 200 mg on the first two days followed by 100 mg daily, have also been used effectively This preparation is most useful for patients in acute status asthmaticus who are unable to take anything by mouth It has the disadvantage of taking longer to act than the oral preparation For the usual patient the schedules above are suitable In status asthmaticus the initial dose recommended is 300 mg given in divided portions of 100 mg each into three different sites in order to promote rapid absorption This should be followed by 50 to 100 mg every six hours until signs of improvement are evident Usually 25 to 50 mg every six hours (100 to 200 mg per day) will be found adequate for subsequent maintenance It is usual to switch to the oral preparation at this stage

Since the demonstration that cortisone is effective orally [67–70] the suspension has been largely replaced by the tablets These are available in tablets of 5 mg and 25 mg The dosage schedules recommended by different authors vary to some extent The following dosages have been reported to be successful 100 mg a day in 25 mg doses at six hour intervals [41 47] 200 mg for the first two days followed by 100 mg a day for an additional five days,[45 63] and 100 to 200 mg daily [36 4] More common is the schedule of 300 and 200 and 100 mg on the first three days respectively [43 49 58 66 69 70] It

is important to note that the higher the initial dose the more rapid the effect Following oral administration relief has been noted as early as one to six hours, although six to twelve hours usually are required This of course is more commonly observed in cases of seasonal hay fever or asthma of moderate severity In the more severe nonallergic cases it may take from one to three days for relief to begin and as long as six to ten days for complete clearing of all symptoms In acute asthma or status asthmaticus Rose Pare and Knight[63] have found an initial dose of 300 mg followed by 100 mg every four hours to be very effective for rapid control of symptoms On this schedule even the very acute case will respond within 12 to 14 hours as a general rule When the patient has become comfortable the dose is reduced to 50 mg every six hours and ultimately to 25 mg if this amount serves to maintain the remission

Studies with hydrocortisone in the treatment of common allergic diseases reveal little difference in results from those obtained with cortisone A difference does exist in the dosage required in that 20 mg of hydrocortisone is approximately equal to 25 mg of cortisone [70]

Duration of treatment depends largely upon the type of case Thus patients with seasonal asthma or rhinitis require treatment only during the pollen season during which time as much as 200 to 300 mg a day in divided doses may be needed to control their symptoms [26] The patient with intrinsic *nonallergic chronic asthma can often be maintained on from 37 5 to 150 mg* a day The duration of such treatment however is dependent upon the other measures employed

There is a difference of opinion regarding the effect of abrupt withdrawal of either cortisone or corticotropin as compared with gradual tapering of the dose In their series of 211 cases treated with corticotropin Rosenberg et al [71] found no difference in the duration of remission whether the medication was abruptly stopped or tapered Carey et al [4] on the other hand have stressed tapering the dose in order to produce a longer remission Differences in the type of case and in the agent used may account for these discrepancies With cortisone it is clear that sudden withdrawal leads to return of the symptoms of seasonal asthma or rhinitis within 12 to 24 hours [26] Most observers recommend gradual withdrawal of cortisone however and from evidence obtained in repeated trials in the same patient it appears that symptoms return more rapidly after abrupt withdrawal Acute respiratory difficulty following abrupt withdrawal of corticotropin has been reported [7] but the report dealt with cases of emphysema not asthma Since cortisone suppresses adrenocortical activity it would seem logical that the tapered dose schedule might allow time for the adrenal cortex to resume normal activity It has been estimated that following the withdrawal of therapeutic doses of cortisone six to ten days are required for the adrenal to react to a test dose of 25 mg of corticotropin as gauged by the eosinophil response and other criteria [73,74]

Duration of Remission The average remission varies with the type of case treated and to a lesser extent with the route of administration of corti

sone. In allergic or seasonal asthma, symptoms usually return within 24 hours after cessation of treatment with cortisone when given orally, or in two to three days when the intramuscular route has been used.[26,46,62] However, much longer periods of remission varying from days to months have been reported for the chronic form of asthma. The average duration seems to be about two weeks, with variations from a few days to as long as nine months.[6,36,44–48,62] In spite of investigations it is still not possible to predict how long a remission can be expected. It is also fairly certain that *duration of treatment and total quantity of cortisone administered bear no direct relation to the length of remission produced.* The one possible exception is the question of gradually reduced dosage schedules versus abrupt cessation, which has already been considered.

Continuous versus Repeated Administration of Cortisone. Some controversy exists regarding the relative advantages of repeated administration compared with continuous use of cortisone. Repeated courses, each averaging 10 to 12 days, followed by an interval of perhaps 2 to 3 weeks without use of cortisone, after which the cycle is repeated, have the advantage of requiring less cortisone in the final reckoning. There is said to be less tendency to gain weight or to develop other side effects which may ensue as a result of continuous therapy.[5,75] On the other hand, such a schedule means that the patient must wait for the symptoms to return—often they return with alarming rapidity—and only then is the next course inaugurated. It is the opinion of the writer that continuous therapy is more advantageous to the patient, provided he or she can be watched periodically. With this mode of therapy there should be no return of acute symptoms and a surprisingly small amount of cortisone may suffice to maintain remission. In some cases as little as 50 mg or occasionally 37.5 mg a day is required. The majority of patients, however, will need 75 to 150 mg, as was stated previously. Under such a regimen it is necessary that certain observations be made periodically. (These are listed in the summary at the end of this chapter.) Another objection to continuous therapy is that the patient may go into a spontaneous remission and cortisone is then administered without need. One can always test the possibility by slowly withdrawing the hormone and, if the symptoms return, resuming therapy unless other measures effectively control the asthma. Self regulation of the dose may occasionally be useful in the hands of an intelligent patient under supervision of the physician. Use of this type of therapy should not be encouraged for the many reasons already given.

Criteria of Improvement. Rather elaborate investigations have been carried out in a number of laboratories in an effort to clarify by objective means the mode of action of cortisone and the actual degree of improvement. These studies included such procedures as daily eosinophil counts, respiratory function tests, measurement of the urinary excretion of steroids, and various other metabolic determinations. The majority of investigators admit[15,36,44,49,65,71,76] that while these procedures are of considerable aid and interest, the best criterion is the clinical response of the patient. For example

the eosinophil count which may be high or within normal limits initially usually responds to cortisone therapy by decreasing one-half or virtually to zero However many patients have improved on moderate doses of cortisone to the extent of becoming completely free of symptoms although the eosinophil count remained fairly elevated in the neighborhood of 600 to 800 cells per cu mm Under these circumstances it is not necessary to increase the dose of cortisone to the extent of producing complete disappearance of eosinophils All that such an augmented dose does is increase the appetite cause weight gain and produce a tendency to edema and rounding of the face—developments which otherwise might not occur Eosinophil counts are quite useful however and will often herald the beginning of a polyarteritis Loeffler's syndrome or in rarer instances tropical eosinophilia It is also probable that if the eosinophil count remains highly elevated in the neighborhood of 1 000 to 2 000 cells per cu mm the case will be difficult to treat and may not even respond to continued high doses of cortisone

Respiratory function tests have been extremely useful in following the changes that occur in pulmonary function They have revealed that cases which might initially have been considered primary emphysema actually were asthma the temporary emphysema being caused by air trapping which is relieved when the bronchospasm and increased bronchiolar secretions are reversed by the effect of cortisone There is as yet little in the nature of a clear cut demonstration that the level of the urinary steroids in particular the glucocorticoids or the 17 ketosteroids offer any particular advantage in guiding therapy [15,44,71,76]

Use of Other Medication in Conjunction with Cortisone Therapy In some of the early reports it was concluded that cortisone and corticotropin potentiated the action of epinephrine and that this preparation should be given with care to the patient receiving cortisone Recent observations have not confirmed this and all usual forms of therapy should and can be used in conjunction with cortisone This includes such preparations as epinephrine by subcutaneous injection aminophylline intravenously or by suppository any of the bronchodilators such as Neo-Synephrine or Isuprel and the usual variety of sedatives Various combinations of theophylline ephedrine and a sedative such as phenobarbital may also be used with cortisone therapy as they frequently decrease the amount of the hormone that would otherwise be required This experience is virtually universal in all the recorded literature Oxygen therapy must be used when essential for cases of status asthmaticus In the case of a dehydrated patient who has been in status asthmaticus for a number of days intravenous glucose or invert sugar solution in water may be given in the usual quantity but it must be remembered that saline is contraindicated

Contraindications

Although there is general agreement regarding contraindications to the use of cortisone no hard and fast rules can be made Some of the conditions mentioned by Kinsell [77] such as the adrenogenital syndrome (in

which corticotropin is contraindicated) and Cushing's disease (in which both hormones are contraindicated) do not occur in association with asthma or hay fever Furthermore, the adrenogenital syndrome is sometimes treated with cortisone in an effort to suppress 17 ketosteroid formation [78] Again one has to evaluate the requirements of each case on its own merits The following conditions should be considered contraindications under most circumstances, but not invariably

Cardiac Failure Because of the already altered salt metabolism and the tendency to edema administration of cortisone will aggravate the condition It is possible to overcome these effects by salt restriction and use of mercurial diuretics When the latter procedure is adopted a potassium supplement must be given not only because potassium excretion may be enhanced by the cortisone but also because the mercurial diuretic lowers the renal threshold for this electrolyte It should be remembered that when cardiac failure occurs in the asthmatic it is usually of the right sided variety, secondary to advanced emphysema and cor pulmonale

Diabetes Mellitus Diabetes and asthma are not commonly seen together Cortisone in moderate doses may induce glycosuria and to a lesser extent hyperglycemia with impairment of the carbohydrate tolerance This effect appears to be temporary in the vast majority of cases Rose Pare and Knight[63] have administered short courses of cortisone or corticotropin to 2 patients with diabetes and asthma without any ill effects A moderate increase in the insulin dosage was necessary to control the blood sugar during cortisone therapy A third patient with diabetes and rhinitis has been on cortisone continuously for two and one half years His insulin requirements have not increased beyond those that would normally be expected in this period of time If a patient has asthma and a family history of diabetes, it is probably best to withhold cortisone or if this is not feasible to test the glucose tolerance frequently Although diabetic coma is undoubtedly a contraindication it has not been seen in association with asthma in this clinic

Peptic Ulcer Perforation of a preexisting duodenal ulcer or the production of an ulcer in a patient who previously was asymptomatic has been reported by a number of observers[68 79—84] who used either cortisone or corticotropin It is of interest that none of the reported cases occurred in patients with asthma or rhinitis In a series of 260 cases of hypersensitivity in which the majority of patients had asthma Rose Pare and Knight[63] encountered one instance of perforated duodenal ulcer in a patient who also had polyarteritis She was maintained on corticotropin therapy throughout operation and with cortisone has remained well since that time[59]—now almost three years Her cortisone requirement varies from 75 to 150 mg a day Nevertheless, the possibility of ulcer should always be ruled out and if there is any question about its presence cortisone should be withheld as emphasized by Bloomfield [85]

Osteoporosis Spontaneous fracture of the bones secondary to osteoporosis is not uncommon in the various forms of arthritis It is not surprising therefore that this condition has been accentuated by the administration of

cortisone or corticotropin in such patients [96] It is well to be certain that the condition is not present before starting cortisone even though it is not common in asthmatic patients Poor diet prolonged bed rest and postmenopausal effects are factors predisposing to osteoporosis in elderly patients

Hypertension One should differentiate between the transient fluctuating hypertension commonly found during acute asthma and hypertension due to other causes The former will respond to cortisone as the symptoms of asthma disappear the blood pressure will fall to within normal limits In essential hypertension on the other hand the blood pressure may not be altered and may even be increased if salt is not withheld Arbesman et al [49] report a case of asthma in a woman who had what appeared to be severe hypertension the blood pressure being 260 systolic 140 diastolic Because of the severity of her asthma corticotropin was administered intravenously Both asthma and hypertension subsided It seems clear that transient hypertension is more apt to occur with corticotropin than with oral cortisone According to Perera [87] oral cortisone may cause a rise in blood pressure if renal damage is present

Pulmonary Tuberculosis Tuberculosis is a complication which must always be anticipated in asthma As in any other infective process administration of cortisone may mask the symptoms and produce subsidence of fever return of appetite and gain in weight Both in man and in animals [88–96] there may be a subsequent flare up and the disease may spread Cortisone has been administered in the presence of tuberculosis under special circumstances Thus in Addison s disease when therapy with cortisone must be maintained complicating pulmonary tuberculosis has responded to streptomycin and p-aminosalicylic acid with complete subsidence of the lesions and disappearance of tubercle bacilli from the sputum Four such cases have been observed at the McGill University Clinic of the Royal Victoria Hospital [97] It is to be emphasized here that 25 to 30 mg of cortisone per day is all that is required to maintain a patient with Addison s disease This is much less than would normally be needed in asthma and it is probable that higher doses would be harmful The presence of healed lesions of pulmonary tuberculosis in a patient with asthma should make one hesitate to use cortisone in high dosage or for prolonged periods However 3 patients with healed pulmonary tuberculosis and associated asthma observed by Rose Pare and Knight [63] received cortisone or corticotropin for periods varying from three weeks to six months without any evidence of a reactivation of the tuberculosis That reactivation may occur is evident from Perchanok s report[93] of a patient with healed pulmonary tuberculosis who was given cortisone for rheumatoid arthritis

Complications of Cortisone Therapy

The complications arising as a result of cortisone administration have not proved to be a serious drawback to its use in asthma or rhinitis Some of these have already been dealt with in the previous section

One gains the distinct impression from a perusal of the literature that the

more serious undesired effects are less apt to occur in asthma or rhinitis but this may result from the fact that patients with other conditions are treated in larger numbers. Hypopotassemia, for example, is rare and, as mentioned previously, perforation of a viscus occurred in but one asthmatic patient.

Perhaps the most common undesired effect of cortisone therapy is an *increase in appetite and gain in weight*. Quite a few patients appear to develop dependent edema which disappears rapidly when the dose is decreased.[13, 26, 36, 4 47, 46] Franklin and Lowell[13] found that edema was produced *more readily by corticotropin than by cortisone but the opposite opinion* has also been expressed.[49] However, the incidence of edema induced by corticotropin does not appear to be higher in other reports[5, 71] of patients treated with the hormones. Such manifestations as acne and moonface are not common in asthma and rhinitis although they have been mentioned.[6, 46, 49, 99] Temporary psychosis[6, 36, 46–49] has been described but is generally not a serious problem. Suicide following treatment with cortisone has been reported in one patient with arthritis.[100] A common and sometime troublesome complaint is insomnia but the condition like all others is temporary and often can be controlled by mild sedation. It is not uncommon for the menstrual cycle to be altered during either cortisone or corticotropin therapy. A single case of convulsive episodes precipitated in a young asthmatic patient by cortisone administration was reported by Lowell et al.[101] No other instances have been encountered in patients with asthma although convulsive seizures have been observed commonly following use of either cortisone or corticotropin in disseminated lupus erythematosus.[65, 70] The spreading of infection by cortisone therapy has been dealt with in the foregoing pages. This possibility must constantly be borne in mind.

In the series of cases observed by Rose, Pare and Knight[63] two cases of spontaneous fracture of the vertebrae associated with osteoporosis were encountered. Both patients were male. One aged 49 with a history of rheumatoid arthritis and asthma of 14 years' duration had been taking daily doses of 100 mg of cortisone orally from March 1950 to March 1951 when the condition developed. A bone graft was performed and he was placed on a schedule of testosterone, calcium, vitamin D and high protein intake. Use of cortisone has been continued and the patient has had no further trouble since the change in schedule. The second patient aged 52 had been maintained on cortisone for four months, when he developed three fractured vertebrae in October 1951. Although usual procedures gave him initial relief the condition has progressed in spite of the fact that cortisone was discontinued.

Only one instance of allergic reaction to cortisone has been encountered[103] and this followed intramuscular administration. The symptoms consisted of nasal obstruction, asthma and swelling of the eyelids and cheeks.

In general all *undesired effects like those changes* which constitute improvement in the disease itself are temporary in nature and disappear on cessation of treatment. They can be prevented by using lower doses for maintenance or, as emphasized by McCombs[52] by interrupting therapy.

Six deaths occurred in the series of Rose, Pare and Knight [63] only one of which could be attributed to hormonal therapy This patient had attempted self medication with corticotropin and was hospitalized with a widespread bronchopneumonia He died within 36 hours of admission The 5 other patients were or had been receiving cortisone but in all of them death was caused by obvious intercurrent disease or complications and no deaths were attributed to the use of this hormone Zoss and Zodikoff[104] reported the death of a 56 year-old man being treated with cortisone Nothing to explain the mode of death could be found at autopsy Sherman[37] also described two deaths neither of which could be attributed to hormonal therapy

Effects of Long Term Therapy

The variety of effects produced by cortisone and corticotropin and the possibility of danger from therapy continued over long periods of time tended to dampen some of the early enthusiasm for these preparations Many of these fears have been dispelled as experience has been gained through the treatment of patients for almost six years In the series of Rose Pare and Knight[63] the patients were checked at regular intervals Laboratory procedures included urinalysis glucose tolerance test and determination of eosinophil response to 25 mg of corticotropin and of the urinary output of 17 ketosteroids and biologic corticoids (glucocorticoids) In no instance has there been evidence of permanent impairment of any of these functions such as might indicate damage to kidney or adrenal cortex All patients received a thorough physical examination X ray examination of chest and spine and electrocardiogram (ECG) when indicated The only permanent change noted was in the asthmatic patient who developed osteoporosis and spontaneous fracture of the vertebrae previously described

McCombs[5] described 5 patients with asthma who were given 12 to 23 separate courses of therapy consisting of either cortisone orally or corticotropin by injection He was unable to detect any damage to these patients in spite of the relatively large dosage of these hormones There were few undesired effects and control was readily achieved In his opinion short courses are preferable to continuous therapy since the tendency to untoward effects is less and the tendency toward Cushing s syndrome or hirsutism is minimal He feels that in general, corticotropin is preferable to oral cortisone There have been similar reports[47 50 64] where continuous treatment over lengthy periods failed to produce any permanent damage Periodic tests and examinations were used as criteria

It seems clear nevertheless that continued administration of corticotropin leads to a temporary hypertrophy whereas prolonged administration of cortisone results in marked but transient atrophy[73 105 106] of the adrenal cortex These observations were based on examination of the gland at autopsy It appears that suppression of adrenocortical activity is associated with a reduction in the substance of the cortex which retains the capacity to return to its former activity once cortisone is discontinued In this connection some observers have advocated alternation of cortisone with corticotropin

in order to stimulate the cortex Although this procedure seems logical it does not appear to have had much effect upon the reaction of the patient or course of the asthma

In the opinion of the author the most important aspect of long term therapy with cortisone relates to the patient with an acute infection or a condition requiring surgery Under either circumstance there may be difficulty of diagnosis since signs and symptoms may be altered or entirely masked by cortisone Secondly the adrenals of the patient treated with cortisone may be incapable of meeting the demands of the situation It is essential therefore that cortisone be maintained at a dosage even higher than before the onset of the acute illness In the case of infection antibiotics are of great value and most patients respond well

Prickman et al [107] describe 4 patients with asthma whose symptoms were controlled by cortisone or corticotropin so that major surgery could be performed Three asthmatic patients underwent major operation without trouble in the series of Rose Pare and Knight [63] The importance of these findings cannot be stressed too strongly With adequate care and an increase in the dosage of cortisone to not less than 300 mg per 24 hours or more if need be on the day of operation most of these patients can withstand surgical procedure Cortisone should be continued in similar dosage for at least three to four days postoperatively and then the dose should gradually be reduced In many asthmatic patients the need may arise for ordinary surgical procedure or such major procedure as lobectomy for bronchiectasis or tumors

The case reported by Fraser Preuss, and Bigford[108] is particularly instructive This patient who had arthritis and had been maintained on daily doses of 50 mg of cortisone orally for a period of months was admitted to the hospital for elective surgery on the hip joint Cortisone was stopped and the operation was performed within 48 hours He withstood the surgical procedure but went into collapse shortly afterward and in spite of all usual measures died within three hours Autopsy revealed pronounced atrophy of the adrenals although the three layers of the cortex were still identifiable on microscopic examination

It is not clear whether the coagulation mechanism of the blood is altered,[108–110] although this possibility should be borne in mind Similarly, interference with wound healing is a possibility [111] but it has not been a major factor

General Effects in Relation to Treatment and Skin Testing

One of the enigmas regarding the effects of cortisone is related to skin tests *Though virtually all mechanisms contributing to or associated with the allergic state are in some manner modified or suppressed the immediately reacting type of skin test is an outstanding exception* This fact enhances the value of cortisone or corticotropin in the initial acute stages of the disease during which symptoms may be rapidly and effectively controlled while investigations can be carried out Thus the immediately reacting skin tests are reliable and can be performed during this stage Similarly, X rays or ECG s are not

initially altered It must be remembered however that *the delayed type of skin reaction such as the tuberculin test or reactions to bacterial vaccines may be impaired or entirely suppressed* The hemogram too will be quite different after initiating treatment in that eosinophils lymphocytes, and the E S R may all be depressed to within normal limits It should be routine, whenever possible to do the hemogram before beginning therapy with cortisone or corticotropin

In the intrinsic type of asthma with purulent sputum within the first 12 to 24 hours of hormonal treatment there will often be an increase in the amount of sputum followed by its rapid reduction or disappearance This initial sputum is very useful to culture for vaccine for subsequent therapy

Although there are few references to the combined use of cortisone with vaccine or hyposensitization therapy the question arises whether cortisone in any way enhances or inhibits the effects of a bacterial vaccine or pollen extract This question which would appear to be most important remains largely unanswered For example no attempt has been made to evaluate the effects of cortisone as an adjunct to pollen hyposensitization by administering small doses of cortisone during preseasonal treatment with ragweed extract Using corticotropin Loveless[11] was able to increase both clinical and conjunctival resistance to ragweed pollen in a patient with atopic dermatitis and asthma Susceptibility was determined by the conjunctival reaction to three grass pollens ragweed and horse dander There were 3 control subjects in the study Although it is difficult to evaluate this single example the report is of interest in that it was possible to administer higher doses of antigen and the clinical course of the patient was improved

The mode of action of bacterial vaccines made from cultures of sputum or nasal smears is not clearly understood In fact many authors feel that the value of such therapy is questionable Nevertheless many patients with asthma of the intrinsic variety appear to derive considerable benefit from this form of therapy If the resistance of the patient is increased and asthma controlled following institution of vaccine therapy it is possible that these effects might be further enhanced by the simultaneous administration of small doses of cortisone or corticotropin Thus it has been routine to inaugurate vaccine therapy and when indicated desensitization in all cases of intrinsic asthma following initial control of severe asthma by cortisone or corticotropin [63] Although some 40 patients on this regimen have been observed as yet no evidence has indicated that either cortisone or corticotropin alters the effects of the injections one way or another

Common Causes of Failure

A small percentage of asthmatic patients fail to respond to either cortisone or corticotropin Some who apparently do not respond to cortisone may improve with corticotropin but the reverse has also been reported At times this may simply be a question of dosage as is evident in earlier reports of patients who responded to 100 units of corticotropin intramuscularly but failed to react to an injection of 100 mg of cortisone [4] It is generally agreed

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150 mg by 1, 200 mg, by 8, and 300 mg by 1 patient The duration of treatment varied from 8 to 71 days A higher incidence of undesired effects occurred in this group than in most others reported This may be related to the higher doses and the duration of treatment required in these cases

Vasomotor rhinitis with and without polyp formation has been studied primarily by Bordley et al [118-120] According to their findings the nasal mucous membranes are restored to normal the sense of smell returns within 72 hours but polyps require some two to three weeks to shrink or disappear entirely They feel that corticotropin is more effective than cortisone in producing these changes Not all authors agree with these findings Baldwin and De Cara [47] and Rose Pare and Knight[63] were unable to verify the disappearance of polyps As in other conditions withdrawal of therapy results in a return of symptoms in from 10 days to 2 or 3 months

Summary

1 Cortisone is probably the most effective agent available for the rapid control of asthma and rhinitis Its effects are temporary and not curative i e upon withdrawal the condition sooner or later will return in the same degree as that existing prior to treatment For these reasons it is imperative that patients be thoroughly investigated and given the benefit of a trial with conventional methods before cortisone therapy is contemplated Use of the hormone should be reserved *for cases of intractable asthma which have not* responded to treatment by recognized means or to tide the severely ill patient over a crisis

2 Since the metabolic and masking effects of hormonal therapy are widespread and varied cortisone should not be used without thorough knowledge of its properties In asthma in particular skin tests of the immediately reacting type are not grossly altered and may be carried out during treatment The delayed type of skin test may be suppressed or completely inhibited

3 As a rule any patient with asthma or rhinitis may receive a trial of cortisone therapy providing no contraindication exists The general precautions consist of placing the patient on a low salt diet supplemented when indicated by potassium Frequent observations of blood pressure urine and weight should be made One must watch for the onset of an infection or the spread of existing infection

4 Of the preparations of cortisone available the oral tablets are most widely used When changing from the intramuscular to the oral preparation it is well to recognize that the former takes from one to three days to exert its effects and that similarly these effects may be prolonged for the same length of time after withdrawal The oral preparation may act within 6 to 12 hours and its effects are dissipated within 24 hours after withdrawal

5 The average dosage for the oral preparation of cortisone is 300 mg during the first 24 hours and 200 mg the next 24 hours then a daily intake of 100 to 200 mg depending upon the response These amounts are conveniently administered in divided doses at six hour intervals When the

today that 40 units of corticotropin is about equal to 100 mg of cortisone or 60 to 80 mg of hydrocortisone

Since a temporary form of emphysema is characteristic of the asthmatic state it is difficult at times to differentiate clearly between asthma and emphysema even when adequate pulmonary function studies are made [111-113] One of the complications of chronic bronchial asthma is obstructive emphysema which may progress to right-sided hypertension with so called cor pulmonale Dyspnea due partially to asthma and partially to true obstructive emphysema will be encountered in such cases It is this type of case which presents difficulties of diagnosis On reviewing reports providing adequate data it is obvious that the majority of poor results occur in patients with emphysema [45 49 63 118]

Another condition which either leads to failure or prevents an average dose of cortisone from exerting its usual effects is infection Thus in asthma associated with pulmonary infection such as bronchopneumonia or a severe bronchitis cortisone not only may fail to suppress the asthma but may allow further spread of the infective process [63] Similarly in an individual maintained on oral doses of 75 to 100 mg of cortisone *a return of such symptoms as wheezing cough and sputum is not infrequently caused by reactivation of an old infection or more commonly the advent of a new infection* The majority of these cases will respond to one of the broad spectrum antibiotics or to penicillin if the patient is not penicillin sensitive

Hay Fever and Vasomotor Rhinitis

Virtually all that has been stated relative to the use of cortisone in asthma is applicable to rhinitis Although the latter is a much less serious condition it warrants as much attention not only because of severe discomfort to the patient but also because it is so frequently a precursor of asthma

Allergic rhinitis whether caused by pollens animal emanations foods, or other external factors can be adequately controlled in most instances with conventional therapy It is clear that a number of those who do not respond may develop asthma during a particularly bad season Reports on allergic rhinitis treated with cortisone or corticotropin are fewer than those on asthma

Generally these cases respond to oral cortisone therapy rapidly but relapse quite quickly if the hormone is withdrawn suddenly It is curious that not a few observers have noted that in patients with both hay fever and asthma the latter responds more readily than does the hay fever [5 6] On the average a dose of 25 mg given every four to six hours in a daily dosage of 100 to 150 mg has been advocated [28 38 44 48 99 117]

In this dosage range relief occurs on the average within 24 hours but has been reported as early as 1 hour after beginning therapy Most observers recommend gradual reduction in dosage since invariable relapse occurs within 24 hours of discontinuing cortisone The daily dosage required for maintenance varies to some extent Thus in the series of 14 patients treated by Stier et al, [6] 100 mg of cortisone was required each day by 4 patients,

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6. Although many tests, such as eosinophil counts, and estimation of respiratory function and of urinary excretion of adrenal steroids have been useful, they have not been as valuable a guide to optimum dosage as have the clinical examination and response of the patient.

7. The duration of remission following withdrawal is generally short in the allergic or seasonal forms of asthma or rhinitis, the average being a day or two. In the chronic nonallergic forms, remission averages one to three weeks, with variations of from one day to nine months. Tapering the dose usually, but not always, prolongs the remission.

8. Short repeated courses are preferred by some observers because the incidence of undesired effects is lessened. Continuous administration may also be used effectively, provided the patient is checked at regular intervals.

9. All other forms of therapy, such as bronchodilators, expectorants, sedatives, or oxygen, may be used in conjunction with cortisone. Their use often hastens recovery and reduces the quantity of cortisone required.

10. The undesired effects of hormonal treatment in our experience have been similar to those described elsewhere in this book.

11. The majority of cases respond to cortisone therapy with rapid disappearance of the symptoms. A few cases appear to be refractory and may respond to corticotropin. The common causes of refractoriness, however, are failure to recognize existing infection or the presence of advanced obstructive pulmonary emphysema.

12. Contraindications to the use of cortisone are marked hypertension, cardiac failure, pulmonary tuberculosis, active ulcer or a predisposition to one, advanced diabetes mellitus, osteoporosis, renal disease, or hypopotassemia. There is no hard and fast rule regarding contraindications.

13. Elective or emergency operations may be performed in asthmatic patients receiving cortisone, provided the dose is adequately increased and then maintained for a period of at least three to four days postoperatively.

14. No permanent damage resulting from the use of cortisone in asthma for periods exceeding two and one half years has been found, with the exception of a single case complicated by progressive osteoporosis with spontaneous fracture of the vertebrae.

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cally manifested in the skin, and antibodies cannot be readily demonstrated in the circulation by any of the usual technics As a result there is no simple laboratory procedure by which the diagnosis can be made or the offending drug identified The diagnosis must be determined from the history of previous exposure the course of the abnormal findings when administration of the drug is stopped and in certain instances readministration of the drug by the same route The use of the patch test in a contact dermatitis is an example, but even in this instance caution must be observed as the reaction may be very severe [3,4]

The clinical picture of allergy to drugs often resembles that seen in serum sickness but the manifestations in the individual patient and the severity and seriousness of the reaction vary greatly Fever may be the only evidence of the process as commonly seen in patients receiving a sulfonamide and the most serious consequence is the diagnostic problem of whether the temperature rise is caused by the underlying infection or by the drug being administered One of the most frequently observed syndromes is the serum sickness type of reaction that may result from penicillin administration in which urticaria, angioneurotic edema fever arthralgia and lymph node enlargement are common

More serious cutaneous involvement such as a hemorrhagic and bullous dermatitis may develop Asthma may be the outstanding feature a typical example being the severe attacks which occur in a patient with chronic intrinsic asthma who is sensitive to acetylsalicylic acid and unknowingly ingests that drug Of increasing importance are those instances of drug allergy in which depression of the activity of the bone marrow results The offending agent is almost always a simple chemical substance and the clinical picture may be characterized by agranulocytosis thrombocytopenia with purpura or depression of all of the elements with a pancytopenia Depression of bone marrow function may also be a toxic effect that is related to the administration of large doses or the result of failure to excrete the substance at the normal rate This situation can be detected by serial blood counts and is reversible when the dose is lowered or the administration of the drug stopped

The allergic reaction however is an all or none event which once it develops is not reversed in simple fashion by withdrawal of the offending drug For this reason once drugs are known to be capable of producing this serious type of allergic reaction they should not be used in repeated courses over long periods of time and should not be prescribed at all unless no other drug is available as an effective substitute An example of a drug known to produce both a reversible toxic depression of bone marrow with excessive dosage and an irreversible allergic type of suppression characterized by thrombocytopenia is chloramphenicol

Experimental Observations

Another serious type of drug reaction is the development of polyarteritis a disease which Gruber[5] suggested in 1925 might be due to hypersensitivity

7

Allergic Reactions to Therapeutic Agents

A. McGehee Harvey

During the past few years the number of chemical substances utilized as therapeutic agents has been increasing and as a result the problem of drug allergy has become important from the viewpoint of both diagnosis and treatment. Reactions to drugs may be of different types. The toxic reaction to a chemical substance depends to a large extent upon the amount administered and is a direct effect which is not related to previous exposure. When functional change such as the development of nausea from the administration of digitalis or tinnitus from salicylates occurs at a lower dose than that given to the average individual it is referred to as *drug hypersensitivity*. Drug allergy, on the other hand, is a specifically acquired alteration in the capacity of a given tissue to react.[1] The stage is always set by previous exposure to the exciting agent or allergen and is never manifested until this latent state is activated by reexposure. In contrast to a toxic reaction it is not definitely related to dosage of the drug and the likelihood of its occurrence cannot be reduced by the administration of a smaller amount of the therapeutic agent.

Types of Reaction

In consideration of the problem of drug allergy there is an important distinction between those therapeutic agents which are proteins and the far greater number which are simpler chemical substances and develop their capacity to act as allergens by forming conjugates with the body proteins. The manifestations of allergy in human beings take two major forms. One is the immediate or urticarial type in which anaphylaxis may occur, serum antibodies are often demonstrable and desensitization is possible. The immediate reaction with flare and wheal to inhalant antigens injected intradermally in the sensitized subject is an example of this type. However, most of the drug allergies are of the delayed or tuberculin type of reaction classi

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swelling and proliferation of venule endothelium was also seen Minimal sludging of blood often appeared four to seven days after the first injection, always becoming more intense immediately after the second injection Cortisone when given prior to the second injection not only produced almost complete inhibition of the reaction, but even after cessation of treatment the vascular changes remained less than in the untreated rabbits when given late it caused residual arteriolar change to disappear Further work may help to determine the amount of risk entailed in continuing a drug after the appearance of allergic manifestations if cortisone is administered simultaneously to suppress the clinical manifestations of the sensitivity reaction

The eye serves as an excellent experimental medium for demonstrating the effects of cortisone or corticotropin given parenterally and of cortisone applied locally to certain inflammatory and exudative reactions which are allergic in nature Three hypersensitivity reactions can be produced in the experimental animal (1) the protein anaphylactic reaction that follows injection of horse serum into the anterior chamber of sensitized rabbits (2) the reaction of bacterial hypersensitivity that ensues when killed streptococci are injected into the anterior chamber of a suitably sensitized animal and (3) the focal reaction which occurs in ocular tuberculosis after the systemic inoculation of large amounts of tuberculin Under appropriate experimental conditions it can be demonstrated[14] that all of these reactions can be either completely inhibited or greatly modified by preliminary treatment with cortisone or corticotropin Further anterior chamber injection of irritating substances to which the animal has never been previously exposed such as glycerin staphylococcus toxin and jequirity infusion will produce iritis This nonallergic inflammatory reaction can also be inhibited by prior administration of cortisone and the injection of this hormone into the anterior chamber along with the irritant will modify the reaction These experiments show that both allergic and nonallergic inflammatory reactions can be controlled by the hormones This emphasizes the fact that the beneficial effect of cortisone and corticotropin in allergic disease including drug allergy need not be dependent upon any specific effect upon antigen or antibody or their interaction

The fact that irritation increases the incidence of sensitization in the animal has been emphasized by Chase and it has been pointed out[1] that potent sensitizing agents should not be used locally when they can be given equally well parenterally for the treatment of a dermatitis Clinical experience with the sulfonamides and with penicillin lends support to these observations Chemotherapy of any type should be instituted only for a cogent reason and the progress of the illness under treatment should be followed closely so that the drug may be discontinued as soon as possible The physician must be thoroughly familiar with the protean manifestations which may signal the development of sensitivity to a drug which he is administering Reactions should be detected in the early stages before they become severe Unless administration of the drug is essential and no appropriate substitute is available it should be discontinued Suppression of the clinical manifesta

Later, Vaubel[6] found lesions compatible with those of polyarteritis in animals which received injections of a foreign protein and Clark and Kaplan[7] noted vascular lesions in 2 patients who had serum sickness at the time of death The relationship was not clear, however until the sulfonamides became widely used and greater opportunity for study of the tissues in drug allergies was afforded Rich and Gregory[8] were the first to demonstrate that the polyarteritis seen in patients with a variety of drug and foreign protein reactions is a manifestation of anaphylactic hypersensitivity The e investigators were able to produce widespread lesions typical of polyarteritis in rabbits by inducing a sensitivity reaction to horse serum This type of polyarteritis has now been described in patients dying as a result of hypersensitivity to iodine thiourea Dilantin and other substances [1] As a consequence the development of manifestations resembling those of serum sickness during the administration of a chemical substance being used as a therapeutic agent is a cause for concern on the part of the physician Serum sickness, resulting from the administration of a foreign protein such as horse serum was once a very familiar picture as long as the administration of the serum had been discontinued in most of the cases before the clinical manifestations became evident, it was usually of no serious consequence Many drugs u ed in modern medicine however are given for prolonged periods, when even minor evidences of an allergic reaction appear the serious question of whether or not the treatment can be continued must be answered

After the initial success in the suppression of the manifestations of certain types of drug allergy in the human subject[9] it was of interest to determine whether or not the anatomic lesions of polyarteritis produced with foreign protein in the animal could be prevented by the administration of cortisone and corticotropin In the first study carried out by Berthrong Rich and Griffith [10] 18 of 20 animals subjected to the serum sickness type of anaphylactic reaction developed cardiovascular lesions similar lesions appeared in only 5 of 20 animals sensitized and given antigen in like manner *but treated with corticotropin In a second series, 16 of 19* rabbits developed polyarteritic and cardiac inflammatory lesions as compared to only 5 of 19 treated with corticotropin [11] Similar studies were done with cortisone [1] and in the three separate studies lesions developed in 51 of 59 sensitized untreated animals and in only 14 of 59 sensitized animals treated with cortisone or corticotropin

Ebert and Wissler[13] have conducted *in vivo* studies of the vascular reaction in serum sickness using the rabbit ear chamber technic in an effort to gain further insight into the pathogenesis of these anatomic lesions described in rabbits Rabbits were sensitized with horse serum some serving for control observations and others being treated with cortisone In the untreated animals localized constrictions and dilatations were seen in the arterioles four to seven days after the first injection of foreign serum and there was segmental sticking of leukocytes to the arteriolar endothelium *Such alterations* were intensified following the second injection, reached their maximum in 12 to 72 hours, and subsided slowly over a period of months Local

rapidly reduced Recurrences after stopping treatment with any of these preparations were infrequent usually mild, and easily controlled by the use of antihistaminic agents A brief case report will serve to illustrate the pattern of response in these reactions

A 39 year old housewife was admitted for mitral valvulotomy On each of several previous occasions he had developed tingling sensations and a red itching eruption on the feet following injection of penicillin Without knowledge of this history she was placed on 400 000 units of penicillin every six hours for five doses following cardiac catheterization but no reaction occurred Later no local reaction was observed following the intradermal injection of 2 000 units of penicillin

Because of these findings the minor nature of her previous reactions and the importance of providing adequate chemotherapy postoperatively she was placed on penicillin On the eleventh postoperative day she developed generalized urticaria and the drug was discontinued During the next two days in spite of large doses of Pyribenzamine the urticaria progressed She complained of sore throat a choking sensation developed chilly sensations mild fever and nausea without vomiting Examination revealed generalized coalescing giant urticarial lesions and angioneurotic edema of the hands feet and face She was given cortisone 100 mg initially and then 50 mg every four hours Within one hour the nausea and sore throat had abated and there was less pruritus and edema with increased mobility of the hands Twelve hours after the first dose she was afebrile the urticaria had disappeared except for small hives at the site of penicillin injections and angioneurotic edema was minimal After 24 hours all manifestations of the reaction had disappeared

Dermatitis Due to Atropine Irritation of the conjunctiva and adjacent cutaneous surfaces as an allergic reaction to atropine is a special situation which may be utilized to illustrate the response of a contact dermatitis to the administration of cortisone and corticotropin Cases have been treated with both hormones with effective results The angioneurotic edema which may accompany poison ivy dermatitis has subsided rapidly in several cases recently treated with cortisone Large doses were used in order to obtain rapid effects for the face was severely involved An initial dose of 100 mg of cortisone was given followed by 100 mg at two-hour intervals for several doses The following case of sensitivity to atropine summarized from the report by Carey and his co workers [9] brings out several points of interest

The patient was a 40 year old white female who had tuberculous uveitis and developed a severe localized dermatitis after the use of atropine for a period of several weeks There was an extensive dermatitis involving the entire left side of the face and extending to the right The lids were swollen and indurated Pericorneal congestion edema of the corneal epithelium infiltrate in the cornea and posterior synechiae were present The skin of the face was red extensively denuded edematous and covered with fresh and crusted exudate Intracutaneous injection of tuberculin produced a strongly positive reaction followed by necrosis and sloughing A patch test with atropine precipitated a severe reaction identical with the facial lesions She received corticotropin intramuscularly every six hours for two weeks (total dose 1 420 units) The cutaneous lesions healed rapidly Erythema and edema subsided in about 48 hours and the raw areas were soon covered with epithelium Corticotropin was continued after healing had taken place and during this period atropine was reinstilled into the conjunctival sac without producing a reaction There was almost complete suppression of the dermal reaction to atropine and to tuberculin during the period of adrenal stimulation

tions during continued administration of the allergen in sensitivity reactions to antipyrine[15] penicillin, p aminosalicylic acid and corticotropin[16] have been reported Until more detailed information is available however, it is not recommended that these be suppressed because of the possibility that a serious and potentially irreversible reaction, such as aplastic anemia or polyarteritis may become apparent only with cessation of hormone administration

Treatment of Drug Allergies

The use of cortisone and corticotropin has proved practical for suppression of the clinical manifestations of drug allergies of the delayed type and of serum sickness and the response to the administration of adequate doses of either hormone has in most instances been prompt and complete The causative agent can usually be identified and withdrawn thus making necessary only a *short period of treatment which is both safe and relatively inexpensive* The results of treatment in the various types of allergy will be presented

Reactions to Penicillin The allergic reaction to penicillin is an example *of drug allergy of the delayed serum sickness type in which the principal* manifestations are in the skin Urticaria and angioneurotic edema have been the chief difficulties in most of the cases treated The urticaria which develops during penicillin administration may subside while the drug is still being given and it may not recur when the same preparation is *readministered* In other instances the reaction is mild and subsides rapidly so that evaluation of therapy may be difficult Of 19 patients treated[16] all had a severe reaction which was increasing in intensity and had not been benefited by other means of therapy *After the oral administration of a single large dose* of cortisone the urticaria improved within two hours Since the urticaria returned in its original degree a few hours later, the change was clearly the result of hormone administration The average total dose utilized was 760 mg with a minimum of 350 and a maximum of 1 000 mg In general after an initial dose of 100 mg 50 mg was administered every four hours for six doses and then 25 to 50 mg every six hours for an additional day In very severe cases in which prompt relief was required the interval between doses was shortened to two hours Cortisone given by mouth is probably the treatment of choice unless the patient suffers from nausea or vomiting

Corticotropin administered by various routes was just as effective in relieving the various manifestations but the rapidity of the relief was not as striking as with cortisone given orally Twenty to forty units of corticotropin was given by intravenous infusion in 1 000 cc of glucose over a period of 12 hours Similar infusions of 20 units were repeated on the second and third day if required In severe cases it may be necessary to continue the infusion longer than 12 hours or to give a supplementary dose of *repository material* in gelatin to prevent escape from the suppressive effect Patients treated with aqueous solution of corticotropin were given 25 to 35 units every six hours until the allergic reaction was under control and then the dose was

which is usually of the delayed anaphylactic type can be effectively blocked by the administration of appropriate doses of cortisone

Of particular interest is the case studied by Brown and Howard [19] of a 63 year old man with diabetes who developed erythema wheal formation and induration about the sites of insulin injection became resistant to the hormone and required approximately 6 000 units a day to prevent the development of severe acidosis During the administration of corticotropin the reactions disappeared and the diabetes was easy to manage with small doses of insulin Within a few days of stopping corticotropin his insulin requirement again rose promptly to very high levels From the detailed studies carried out in this patient it seemed clear that corticotropin did block the allergic reaction to insulin which had apparently interfered with its physiologic action

Hematologic Alterations In several instances in which agranulocytosis followed the administration of a sulfonamide treatment with cortisone or corticotropin[9, 20] produced a rise in the total white cell count and in the number of granulocytes It is extremely difficult however to draw any conclusions from the limited data available because control observations cannot be made safely in such cases In the type of bone marrow depression in which thrombocytopenia predominates large doses of either hormone may have a beneficial effect upon the hemorrhagic tendency but in most cases observed the rise in the number of circulating platelets that may occur is not maintained when hormonal therapy is discontinued

Individual case reports of the treatment of allergic reactions to a variety of other drugs are available It seems clear that these hormones can effectively suppress the clinical manifestations in drug allergies of the delayed serum sickness type and thus at least shorten the period of discomfort for the patient They also seem beneficial in certain of the more serious reaction such as exfoliative dermatitis and possibly in agranulocytosis The study of allergic reactions to drugs is an important field Further observations on the effects of cortisone and corticotropin in the various reactions observed in the human subject may yield important basic information concerning the nature of these disturbing complications

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Exfoliative Dermatitis One of the most serious types of drug allergy is the development of exfoliative dermatitis, a well known complication of the use of arsenicals in the treatment of syphilis Of the drugs in current use on a reasonably extensive scale penicillin, sulfadiazine streptomycin, phenobarbital and trimethadione have also been known to produce this reaction As this complication may have a fatal outcome its early detection is important, the offending agent must be withdrawn promptly and intensive therapy with cortisone or corticotropin is indicated The choice of hormone and the route of administration will depend upon the basic disease for which the responsible drug was being given and the extent and location of the involvement of the skin and mucous membranes There are few detailed reports of cases of this type treated with cortisone or corticotropin, but the following summary of a case of exfoliative dermatitis due to iodine originally reported by Carey and his colleagues,[9] demonstrates that these hormones may produce a rapid change in the course of the illness

The patient was a 34 year-old laborer who developed an erythematous maculopapular eruption on the twenty fourth day of therapy with hydriodic acid Three days later the medication was discontinued and on the following day his temperature rose to 105 the eruption became confluent and ulcerative lesions developed on the mucous membranes of the mouth with extensive angioneurotic edema Extensive exfoliation developed he was disoriented and the fever persisted Corticotropin was started at the height of the illness when he appeared moribund and doses of 25 units were given intramuscularly every six hours After two days the temperature was normal and the edema had largely subsided He became more alert and within a few days all of the denuded areas showed epithelization Five days after discontinuing the corticotropin he had a relapse with recurrence of exfoliation but responded well to resumption of hormone administration

Serum Sickness Eight patients with serum sickness, due in 7 to tetanus antitoxin and in 1 to diphtheria antitoxin, have been treated with cortisone or corticotropin by Shulman Schoenrich and Harvey [16] The dose of cortisone was 100 mg orally followed in four hours by 100 mg and then by 50 mg every four hours for six doses The total dosage of corticotropin given intramuscularly averaged 300 units the initial dose varying from 25 to 50 units Several cases were treated with corticotropin by intravenous infusion, 40 units being given over the first 12 hour period There was prompt and complete response to treatment in all of the cases Two of the patients showed evidence of involvement of the nervous system and recovered without loss of function The early use of cortisone or corticotropin is particularly recommended when evidences of nervous system involvement appear

Reactions to Hormones Certain of the therapeutic substances which are widely used are proteins and are probably complete antigens such as insulin and corticotropin in contrast to most drugs which are simple chemicals and must form conjugates with body proteins before sensitization occurs Shortly after the release of corticotropin in 1949 allergic reactions to it were reported by Traeger [17] and later by Brown and Hollander [18] It has been demonstrated by Shulman Schoenrich and Harvey [16] that this allergy

8

Diseases Affecting the Skin

Donald M Pillsbury and Frederick Urbach

In no group of diseases are the effects of cortisone and corticotropin more striking than in some of the conditions affecting the skin Since the lesions are visible and the reversal to normality is rapid in some processes the effects of such treatment are remarkable particularly to any physician who has had to deal *with many cases of chronic dermatoses for which no satisfactory* method of treatment was previously available However these effects have led to rather sweeping premature endorsement of adrenocortical therapy in a variety of skin conditions and considerable revision of early conclusions has become necessary Moreover it is apparent that these hormones are being used increasingly in some skin conditions which are so mild and inconsequential as to make employment of this method of treatment ill advised

Of the greatest importance is the judgment of the individual physician with respect to the wisdom of administering any treatment which is effective in a wide range of diseases yet may produce undesired effects One may adhere strictly to the axiom that the possible ill effects of a method of treatment must never exceed the potential ill effects of the disease being treated It has been argued that cortisone and corticotropin should be employed only for the treatment of fatal diseases However we are not willing to subscribe to this view for as Rothman[1] has well stated some diseases do not take life they just ruin it Certain skin conditions such as generalized exfoliative psoriasis atopic dermatitis and generalized seborrheic dermatitis rarely cause death On the other hand they may produce complete disability wreck the social and family life of the unfortunate patient, and act as a source of psychic trauma from which he may never recover Such patients will inevitably grasp at any method of treatment which offers hope of surcease and may be willing—to the point of insistence—to assume risks somewhat greater than the physician deems advisable Under such circumstances

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allergic mechanisms antibody formation collagen ground substance and hyaluronidase

Adrenocortical therapy is of most immediate practical value in those dermatoses proved or suspected to be of allergic origin Study of the alterations in allergic mechanisms produced by cortisone and corticotropin has so far led to the conclusion that there is no clinically significant reduction in antibody production and no demonstrable action on the union of antigen and antibody The beneficial effect seems to take place at the cellular level perhaps by alteration of cell membrane permeability or interference with the action of whatever noxious agent is produced by antigen antibody union [3]

The immediate cutaneous wheal type allergic reaction presumably mediated by thermolabile reagin is not affected by administration of cortisone or corticotropin [4] but the delayed granulomatous skin response due to sessile (cellular) antibodies is frequently depressed although not completely inhibited [5] Epicutaneous patch tests in patients with contact dermatitis also are not affected except in high dilutions even though it is believed that the antibody responsible for these reactions is a sessile one [6] As might be expected from the observation that these hormones reduce vascular damage but do not interfere with circulating antibody it has been reported that they inhibit the Shwartzman phenomenon [7] but development of the phenomenon of Arthus which is an expression of hypersensitivity mediated by circulating reagin is not affected [8] The conclusion that cortisone and corticotropin act at the cellular level is entirely compatible with the observation that their beneficial effects are the result of suppression of the symptoms but not of cure of the underlying allergic disease

Cortisone and hydrocortisone are thought by some investigators[6] to be absorbed through the mucous membranes of animals and humans and through the very thin skin of small experimental animals such as the mouse [9] Their anti inflammatory effects may be readily demonstrated in the conjunctiva and nasal mucosa Unfortunately the results of topical application of cortisone (though not hydrocortisone) to human skin have been disappointing This may be caused in part by difficulty in absorption of this steroid through the relatively thick human skin In the mouse topically applied cortisone causes thinning of the epidermis cessation of hair growth and decrease in size of the sebaceous glands The thickness of the skin is reduced apparently through a loss of substance from the collagenous fibers This effect appears to be temporary and the mouse skin eventually becomes refractory to the local effects of cortisone if application is continued long enough [9] Intradermal administration of cortisone and hydrocortisone in doses too small to cause systemic effects results in decreased cutaneous reactivity *to the delayed type of allergic response such as the insect bite* reaction [10]

Some diseases affecting the skin are fatal Most serious of these are the collagen diseases (visceral lupus erythematosus diffuse scleroderma, polyarteritis) and pemphigus which often are dramatically improved by adreno cortical therapy In the collagen diseases connective tissue is primarily

the physician may be called upon to exercise judgment for which no set rules will be entirely satisfactory In this discussion of the treatment of various dermatoses with cortisone and corticotropin, we shall attempt the formulation of certain broad rules based on selected published experiences and personal experience with some 300 dermatologic patients to whom these hormones have been administered In some conditions it is possible to answer the question as to the advisability of instituting hormonal therapy with "Yes always, or ' Only under certain conditions," or ' Hardly ever" or "Never , but in others a categorical opinion cannot be given

It has unfortunately been well established that adrenocortical therapy of and by itself does not cure disease, though it may completely suppress all evidence of it for a time This effect has been named ' morbidistatic ' by Sulzberger, in analogy with the terms bacteriostatic and fungistatic In the treatment of diseases affecting the skin it is essential that this limited and temporary effect of cortisone and corticotropin be kept constantly in mind In a skin disease in which the cause is operative for only a short time as in a severe drug eruption, adrenocortical therapy will appear to be curative because it suppresses evidence of disease until the cause *if accurately determined* can be removed In serious disease states such as acute disseminated (visceral) lupus erythematosus or pemphigus the reversible inflammatory and systemic manifestations of the disease (though not the structural changes) may ordinarily be brought under control by cortisone or corticotropin therapy in the hope that the patient may be kept alive until some remission of his disease occurs It is worthy of note that in these and some other diseases it has not previously been possible to keep patients alive long enough to determine whether or not a permanent remission ever occurs In disease states such as atopic dermatitis hormonal therapy is reserved entirely for the control of fulminating widespread flare ups of the inflammatory process in the justified hope that a prolonged remission of the disease will eventually occur spontaneously

Certain general questions some of them not fully answerable on the basis of present knowledge must be asked before hormonal therapy is given for any di ease affecting the skin These are as follows (1) Is the calculated risk of such therapy worth assuming? (2) Is the hormone effective in the skin disease to be treated? If so is the control ordinarily partial or complete? (3) Is the condition to be treated self limited or may partial or complete remission of the disease be obtained either spontaneously or from other types of therapy? (4) Is it likely that hormonal therapy—once instituted—will have to be continued for weeks months or even years? If so is it likely that the necessary dose will be small or large

Experimental and Theoretic Considerations

The diseases of the skin in which adrenocortical therapy ha proved to be of most benefit have in common one or several abnormalities which are affected by the e hormones Thus it is appropriate to review briefly the present knowledge of the influence of cortisone and corticotropin on

in some patients but ordinarily it proceeds quite normally Due considera tion should however, be given to the taking of biopsies in scarred areas or in regions where the adequacy of the peripheral vascular system might be questioned Under any circumstances the taking of large 'surgical biopsies with the inclusion of a considerable wedge of tissue probably offers little advantage in most dermatologic cases and should be avoided

Effects of Hormonal Therapy

In considering the effects of cortisone and corticotropin upon various diseases affecting the skin it is convenient to divide the conditions into the following groups (1) diseases of serious medical import, in which the skin is frequently or always affected and cortisone or corticotropin is useful in varying degree, (2) nonfatal skin diseases capable of producing prolonged, partial, or complete disability (3) acute relatively self limited diseases affecting the skin in which the symptoms and disability may be mild to extreme (4) other diseases of various types affecting the skin in which corti sone or corticotropin is rarely indicated

Acute Disseminated Lupus Erythematosus Chronic Discoid Lupus Erythematosus Acute disseminated lupus erythematosus is considered in detail elsewhere in this volume (Chapter 5) A few remarks may be in order, however particularly with respect to the differentiation of some benign conditions of the skin which are commonly the source of a mistaken diag nosis of visceral lupus erythematosus

Visceral (acute disseminated) lupus erythematosus with characteristic skin lesions has been recognized as a serious medical disease for some 75 years During the past 15 years much new information has become available with respect to visceral lesions of the disease the hematologic picture par ticularly the L E cell changes in the serum protein and the presence of biologic false positive tests for syphilis This knowledge has permitted a diagnosis of visceral lupus erythematosus to be made accurately in the absence of characteristic skin lesions It has also served to increase the index of suspicion toward the disease until it would now sometimes appear to be entertained almost too casually as a diagnostic po sibility

One frequently encounters patients in whom a diagnosis of visceral lupus erythematosus has been made because of the occurrence on the face of the skin lesions of other diseases The most common sources of error are sebor rheic dermatitis rosacea chronic erythema multiforme photosensitivity and chronic contact dermatitis Some confusion has also arisen because of the tendency to use the word lupus without qualification as a diagnostic term Lupus vulgaris is a form of tuberculosis of the skin uncommon in the United States but common in parts of Europe Chronic discoid or better, *cutaneous* lupus erythematosus is a relatively benign disea e affecting the skin and mucous membranes only acute di seminated or better *visceral* lupus erythematosus is a serious disease affecting all parts of the vascular tree in which involvement of the skin is relatively incidental and may not occur

affected but the pathology of pemphigus is manifested by lack of cohesion of the basement membrane of the epidermis to the corium Knowledge of the action of cortisone and corticotropin on the mesenchyma is thus of the utmost importance in the understanding of their beneficial effects in these syndromes

Cortisone and corticotropin appear to affect connective tissue by (1) suppressing osmosis through semipermeable membranes (2) decreasing permeability of capillaries (probably indirectly) (3) decreasing the spreading effect of hyaluronidase probably by acting on the hyaluronate substrate, (4) reducing the number of fibroblasts and production of collagen fibers perhaps through interference with the synthesis of chondroitin sulfuric acid, (5) exerting a catabolic action on proteins eventually resulting in reduction of antibody titers by interference with gamma globulin synthesis

It appears that these hormones may be effective in collagen diseases by decreasing the permeability of connective tissue membranes thus interfering with the exchange of components between blood and tissues enhancing protein (and thus antibody) catabolism promoting maintenance of connective tissue and reducing proliferation of fibroblasts and collagen fibers [11]

The effect of hormonal therapy upon infection particularly in producing activation and dissemination of a chronic infection such as tuberculosis or in the suppression of signs and symptoms of a severe internal infection is considered in detail elsewhere in this book There is a considerable volume of experimental work to indicate that such therapy may have an adverse effect during the invasive phase of a new bacterial or virus infection [1–15] Because of these facts many investigators have been cautious in the treatment of patients with evidence of chronic or acute superficial bacterial infections of the skin We have observed no adverse effects clinically in such patients However in the presence of impetigo an infected ulcer or cellulitis administration of appropriate antibacterial therapy is obviously wise before hormonal therapy is considered In chronic low grade bacterial infections which are a common feature of long standing skin diseases such as atopic dermatitis seborrheic dermatitis and nummular eczema the bacterial infection may safely be disregarded in the consideration of whether or not cortisone therapy should be given We have observed no dissemination of such infections following hormonal therapy in fact the effect is ordinarily beneficial In such patients if the integrity of the skin can be restored to normal it may be possible to control the chronic infection almost completely though pathogenic bacteria may be recovered for long periods of time from skin which is seemingly normal

Another consideration which frequently arises with respect to patients who are being treated with cortisone or corticotropin is whether or not a biopsy or other minor surgical procedure should be undertaken because of experimental data indicating interference with healing and formation of granulation tissue in experimental wounds [16] It has been our experience that the taking of small punch biopsies presents no hazard to patients who are receiving hormonal therapy Healing of the area may seem slightly delayed

Pemphigus Pemphigus is a characteristic bullous disease of the skin and mucous membranes which is of extreme chronicity Until cortisone and corticotropin became available it was always fatal within months or a few years Aside from occasional involvement of the adrenal gland the visceral lesions early in the disease are extraordinarily minor, but in terms of distress and discomfort to the patient relentless chronicity and the necessity for constant nursing care, hardly any disease in medicine is more formidable

A complete review of the disease will not be attempted here For detailed information the reader is referred to the excellent monograph of Lever[23] Briefly, the salient features of pemphigus are as follows

(1) Large flaccid bullae develop on normal or slightly erythematous skin leading to denudation and granulating erosions Lesions on the mucous membranes of the mouth and vagina are common

(2) The lesions usually appear first around body orifices on pressure sites and in intertriginous areas There is gradual at first remitting then steadily progressing involvement of most of the cutaneous surface

(3) Rapid debilitation occurs after the mucocutaneous involvement becomes extensive with marked hypoproteinemia anemia cachexia due to dysphagia and protein loss and death due to inanition or serious systemic secondary infection The disease is almost uniformly fatal

(4) The lesions are characterized histologically by acantholysis A simple diagnostic technic that has been described[24] consists of Giemsa staining of scrapings taken from the base or edge of a fresh bulla In pemphigus the smears show large sheets and clusters of rounded epithelial cells which have lost their prickles have a relatively large oval nucleus and show condensation of the cytoplasmic nucleoprotein around the periphery of the cell This gives the appearance of a bluish halo around the cell margin separated by a lighter staining protoplasmic ring from the nucleus This phenomenon which is almost always demonstrable in smears taken from early pemphigus bullae appears to be of diagnostic significance since it reflects the basic tissue defect namely acantholysis The characteristic features are even more clearly demonstrable in full thickness biopsies of affected skin or mucous membranes

In summary the striking features of the disease are predilection for elderly males of middle European or Jewish extraction early involvement of the oral and pharyngeal mucous membranes flaccid rapidly eroding bullae with little tendency to spontaneous healing and marked debilitation

TREATMENT All types of pemphigus respond favorably to cortisone and corticotropin therapy *provided adequate doses are given* The dosage required in severe cases is often very high Improvement may be striking but no sustained remissions have been reported It is necessary to administer one of these compounds either continuously or in repeated courses Because of the high doses required and the prolonged course of therapy undesired hormonal effects are frequent and continuous vigilance is necessary

The following case report demonstrates certain features which are frequently encountered in the management of pemphigus (1) The diagnosis

In some patients the differentiation of visceral lupus erythematosus from the cutaneous type, or from photosensitivity, may be extremely difficult It is obviously of the greatest importance from the standpoint of prognosis, however, and crucial to the decision as to whether or not cortisone therapy is to be employed It is our opinion that the differentiation between the visceral and nonvisceral types of lupus erythematosus may ordinarily be made promptly in at least 95 per cent of patients Chronic discoid lupus erythematosus may remain for many years as a disease of extraordinary tenacity It seems probable that adrenocortical therapy offers nothing toward permanent "cure" of chronic discoid lupus erythematosus[17,18] whereas in the acute disseminated type such therapy may afford striking relief Furthermore it would appear that in discoid lupus erythematosus other methods of treatment, particularly atabrine or chloroquine[19-21] are far more effective than cortisone or corticotropin In occasional patients the diagnosis may remain in doubt for some time possibly for years because of the extent of the skin lesions which clinically and histologically seem characteristic of chronic discoid lupus erythematosus and because vague suggestions of visceral disease are present without decisive clinical or laboratory signs It is our opinion that in such patients bismuth therapy is hardly more than a placebo injection of gold salts is contraindicated and the immediate administration of cortisone or corticotropin is inadvisable The status of atabrine therapy is at this time not completely determined but it would appear that it is considerably more effective even temporarily than cortisone or corticotropin in discoid lupus erythematosus Preliminary experience would indicate that chloroquine may be fully as effective as atabrine and more acceptable to patients because it does not produce objectionable pigmentation of the skin

Generalized Bullous Eruptions of the Skin Because of their relatively rapid onset, the tendency to denude large areas of skin the frequency of serious (superficial or systemic) secondary bacterial infection rapidly progressing debilitation and the difficulties encountered in differential diagnosis and management the generalized bullous diseases of the skin represent one of the most important groups of cutaneous disorders Three major categories have been recognized (1) pemphigus (2) dermatitis herpetiformis and (3) erythema multiforme–like eruptions Their etiology is unknown but in erythema multiforme many different factors including drugs virus and bacterial infections systemic toxicity secondary to neoplasms irradiation and allergic sensitivity, may be operative

The cutaneous and other manifestations of these diseases are often very similar, and accurate diagnosis may be difficult However because the eventual prognosis and response to therapy vary greatly proper classification is of great importance

Cortisone and corticotropin have revolutionized the therapy of the bullous diseases Until 1949 pemphigus was a universally fatal disease with these hormones it is now possible to restore many patients suffering from pemphigus to a useful and reasonably comfortable life for periods still to be determined

marked psychologic benefit if he were discharged from the hospital and allowed to return every other day for the intravenous corticotropin therapy

Following discharge the patient did fairly well for about two weeks Because of the difficulty of transporting him to the hospital every other day for corticotropin infusions 200 mg of cortisone given orally in divided doses each day was substituted On this amount of hormonal therapy the patient gradually became worse and new lesions developed rapidly with marked superficial sloughing and pain of the oral mucosa Because of uncontrollable secondary infection of the skin by Proteus vulgaris and the development of severe dependent edema the patient was readmitted to the hospital on February 13 1952

About half of the cutaneous surface had become denuded There was much secondary infection and the patient was extremely weak It was obvious that a considerable amount of the patient s edema and weakness were symptoms of a hormone induced salt and water retention Consequently therapy was changed to corticotropin 40 units intravenously by 8-hour drip a salt free diet and copious use of mercurial diuretics Under combined corticotropin acetarsone antibiotic local and diuretic therapy the patient improved markedly and was discharged in March 1952

Following discharge the patient was at first treated with daily and later tri weekly corticotropin intravenously Various long acting corticotropin preparations were gradually substituted Until September 1952 he remained almost completely asymptomatic regaining strength and being able to work Following a mild upper respiratory infection new flaccid bullae appeared on the face and lip margin Increase of corticotropin dosage from 35 to 50 units of long acting hormone per day caused no improvement even though a Thorn test showed good adrenal response Addition of 160 mg of hydrocortisone daily by mouth resulted in gradual clearing of lesions

In January 1953 it was noted that the patient had developed a persistent hypertension of 180 to 210 mm systolic and 100 to 120 mm diastolic and a grade 2 hypertensive retinopathy Also the fasting blood sugar was abnormal for the first time being 305 mg per 100 cc of blood Urinalysis showed 4+ albumin 1+ sugar and a trace of acetone In view of the glycosuria and fasting hyperglycemia this was felt to be a true diabetes made worse by the hormonal therapy Dietary control and insulin therapy were instituted Under a regimen of corticotropin insulin low salt diet and potassium chloride the patient is now again asymptomatic

Worthy of note is the fact that the patient developed persistent hyperpigmentation in all areas previously denuded by pemphigus lesions and that the previously almost white chest hair has again become black

As can be seen the over all result in this patient who was almost moribund on admission has been excellent Yet he suffered almost all the complicating effects of hormonal therapy so far reported

In our experience corticotropin is preferable to cortisone in the management of pemphigus Given intravenously 1 unit of corticotropin has the equivalent activity of 15 to 25 mg of cortisone given orally and the newer long acting preparations of corticotropin have an effect almost equal to that obtained with intravenous corticotropin (8 hour drip) The usual regimen has been to start with 25 to 40 units of corticotropin intravenously by 8 hour drip daily until improvement is marked and then change to long acting corticotropin 35 to 50 units intramuscularly once daily When patients are almost asymptomatic and at least two weeks after the formation of new bullae has ceased the dose of corticotropin is gradually reduced usually by giving 35 to 50 units every other day and then by decreasing the individual

may be delayed until considerable debilitation of the patient has occurred (2) Cortisone is less effective than corticotropin in pemphigus (3) The nursing care of patients with extensive pemphigus is difficult and often extremely obnoxious (4) Such patients are susceptible to a wide variety of bacterial infections (5) The dose of corticotropin necessary to control pemphigus may be very high, and the risk of untoward physiologic effects must be accepted

Case Report

M M a 59 year old Armenian printer consulted us on July 8 1951 In December 1950 the patient had developed redness and soreness of the tongue Bland local therapy and injections of penicillin did not result in any improvement By February 1951 bullous lesions and ulcerations had developed on the mucosal surfaces of the mouth and nose and the perioral and perinasal skin A diagnosis of moniliasis was made on the basis of a skin culture By May the bullous dermatitis involved the lower legs ankles elbows and abdomen When seen by us in July the patient was immediately hospitalized because of generalized denudation of the skin and severe debility resulting from marked dysphagia The past medical and family history and systemic review were not contributory

Treatment was begun with 25 units of corticotropin in 1 000 cc of 5 per cent dextrose in water Initially this was administered daily through intravenously inserted polyethylene tubing In addition the patient received 250 mg of aureomycin four times daily For the next 10 days the patient showed slight improvement but continued to have a diurnal fever ranging to 101°

On July 16 1951 the patient was placed in a bathtub for the purpose of removing some of the crusts from his skin The next day the temperature was elevated to 105 6 rectally and he suffered from chills and apprehension A blood culture taken at that time revealed a paracolon organism 50 colonies per cc of blood The patient was given neomycin 0 5 Gm intramuscularly twice daily penicillin 1 000 000 units every 3 hours and streptomycin 1 Gm daily Corticotropin therapy was stopped at this time For the next three weeks the patient was extremely ill and the immediate prognosis appeared poor Vigilant and devoted nursing care was a crucial factor in keeping the patient alive A blood culture taken on July 21 showed no growth and neomycin was discontinued The patient continued to have a moderate fever of about 101 until corticotropin therapy was reinstituted Beginning in early August a fairly constant albuminuria varying from a trace to 2+ was noted Slight transient glycosuria was also present From August 2 until October 11 the patient received 25 units of corticotropin intravenously every other day About the end of September he began to show fairly steady improvement with moderate clearing of the skin though occasional new bullae were seen Slight increase in strength and appetite was noted During this time a severe thrombophlebitis of the right leg developed which resulted in severe edema of the ankle and leg

Early in October the patient was permitted to sit up in a chair for the first time since his admission His weight at this time was 124 lbs On October 11 the dose of corticotropin was reduced to 15 units every other day and this was continued until October 15 However during this time he had a severe exacerbation of acute bullous lesions From October 17 he was again given 25 units of corticotropin every other day For the next few weeks recovery was slow and occasional new bullae still formed However the patient steadily gained weight and strength and became fully ambulatory by the end of October At this time he was receiving 600 000 units of penicillin daily This had been stopped temporarily in the middle of October but shortly thereafter a monilial and bacterial infection of the skin developed and the penicillin was resumed By mid November body weight had increased to 139 lb and marked gain in strength was noted It was felt that the patient would receive

pemphigus Daily doses of 200 to 300 mg of cortisone with rapid reduction of the dose thereafter or 15 units of corticotropin intravenously every eight hours appear to be sufficient to induce quick remissions If it is possible to discover and control the causative agent relapses are not common In cases

Table 3

DIFFERENTIAL DIAGNOSTIC TABLE OF BULLOUS ERUPTIONS*

	Pemphigus	*Dermatitis Herpetiformis*	*Erythema Multiforme*
Type of bulla	Flaccid small to large	Grouped vesicles (herpes like)	Tense very large
Erosions	Large due to peripheral extension	Excoriations only	Ordinarily small
Healing of erosions	Little tendency to spontaneous healing	Good	Good
Presence of oral lesions	Always	Rare	Up to 20% depending upon type
Degree of oral involvement	Usually severe	Mild	Usually mild
Involvement of vermilion border of lips	Common	Very rare	Uncommon
Race	Middle European and Jewish	No predilection	No predilection
Usual age of onset	50+	Young adults	Any age
Mortality before cortisone and corticotropin	95%	Very rare	Up to 20% depending upon type
Histology	Acantholysis intraepidermal bullae	Subepidermal vesicle	Subepidermal vesicles
Serum chemistry			
Albumin	Considerably decreased	Normal	Slightly decreased
Sodium	Considerably decreased	Normal	Normal
Chlorides	Considerably decreased	Normal	Normal
Response to cortisone or corticotropin	Usually good but huge doses often required Maintenance doses needed for long time Better response to corticotropin	Doubtful response to either hormone	Excellent response to small doses of either hormone

* This table is based upon data contained in the article of Lever [23]

in which the etiologic factor is not determinable however recurrences may be brought under control as easily as the primary attacks Undesired effects are not common because the dosage required is usually not large and the necessary duration of therapy rarely exceeds four to eight weeks

dose In most of our patients a well defined minimum dose below which bullous lesions gradually recur has been determinable In addition all patients are given 3 Gm of enteric coated potassium chloride daily and a low salt diet After discharge from the hospital, they are checked regularly for elevation of blood pressure edema and hyperglycemia Local therapy, such as baths and antibiotics, is given as indicated During the acute phase of the disease transfusions of blood red cells, or plasma are given as well as such protein sparing drugs as methyltestosterone

In almost all of the patients whom we have treated for pemphigus, continuous therapy without rest periods has been necessary It appears that relapses may become progressively more difficult to control and should be prevented if possible How long it will be possible to maintain pemphigus patients in reasonably good health cannot be predicted at this time but at the end of almost two years of experience, we continue to be hopeful

Erythema Multiforme–Like Bullous Eruptions There has been an apparent increase in incidence in this group of diseases Since many such eruptions are presumably caused by drug sensitivity and the number of commonly used drug sensitizers has been increasing more than exponentially this is not surprising

The most important features differentiating erythema multiforme from pemphigus are

(1) The onset is generally very rapid Widespread cutaneous involvement occurs, with tense often large, bullae arising on erythematous or urticarial skin The erosions are ordinarily small, do not spread by extension, and heal rapidly unless much secondary infection is present Mucosal involvement is not as common as in pemphigus, and, if present, differs by a tendency to spare the vermilion border of the lips Fever is common

(2) The disease is usually acute and lasts for a few weeks, as a rule Recurrences are sometimes traceable to readministration of a drug but the exact pathogenesis often remains obscure

(3) The syndrome is more common in younger age groups and may occur in children (Stevens Johnson type) The mortality is low Debility is not a prominent feature unless other systemic disease is present

(4) The chief features are acute onset, often relatively few systemic symptoms sometimes a history of drug administration infection or preexisting systemic disease self limited course in most cases and a low mortality rate

(5) No acantholytic epidermal cells are seen in smears but many polymorphonuclear and eosinophilic white blood cells and fibrin debris are present

One type of bullous eruption probably belonging in this group and important because of its similarity to pemphigus is the so called 'bullous pemphigoid' [22] For features of differential diagnosis see Table 25

TREATMENT Patients with erythema multiforme–like bullous eruptions usually respond quickly to either cortisone or corticotropin The dosages needed to control the disease are much smaller than those required in

or corticotropin such treatment appears to present little or no possibility of undesired hormonal effects

Contact Dermatitis The clinical characteristics of a sensitivity reaction to a common contactant such as poison ivy are well known The initial reaction is one of erythema and vesiculation most commonly on exposed portions of the skin with in males frequent appearance of dermatitis on the genitalia by transfer of the contactant with the hands A striking characteristic of any contact dermatitis is that long haired areas, particularly the scalp are not commonly involved The palms and soles are likewise infrequently involved not as is commonly believed because of the thickness of the skin but because of the absence of hair follicles through which the allergen reaches the living cells of the epidermis In severe contact dermatitis coalescence of vesicles may occur with formation of large bullae Itching is a constant feature There may be extreme edema not infrequently the face is affected to the degree that the eyes cannot be opened Fever may be present in severe cases Sufficient absorption of the allergen may occur or may combine with proteins in the skin and produce dermatitic and urticarial lesions at sites removed from the principal areas of contact Significant involvement of internal organs is not usual unless there is secondary infection or the patient is overwhelmed by treatment with specific antigens

The distribution of contact dermatitis may vary greatly The possible role of a contactant *in a dermatitis is frequently overlooked and should* always be considered Chemicals capable of producing contact dermatitis have increased possibly a hundredfold in the last 15 years Thousands probably hundreds of thousands of reactions have occurred from the local application of such substances as penicillin streptomycin sulfonamides local anesthetics and antihistaminic drugs The first three groups of compounds should assuredly never be applied topically in the treatment of diseases of the human skin Certain antihistaminics are known to have such strong sensitizing effects as to preclude their usefulness and it is doubtful whether the local application of any antihistaminic compound is justified on the basis of either curative effects or risks of sensitization of the skin We do not prescribe them Further we do not advise the topical use of any local anesthetic which is chemically related to procaine

In addition to these and other medicinal agents hundreds of skin sensitizers have found usefulness in industrial processes in new fabric materials in cosmetics and in various preparations used around the house particularly insecticides and detergents The reactions to these compounds may produce syndromes which are at times very puzzling

Cortisone regularly effects prompt control of dermatitis due to an external contactant Because it is not necessary to administer the hormone for more than a few days at most in such a reaction the occurrence of undesired effects is infrequent Nevertheless it is obvious that the use of cortisone should be reserved only for contact dermatitis which is severe and disabling

In *severe* contact dermatitis we have used the following dosage regimen

Dermatitis and Eczema On the basis of admissions to U S Army hospitals during World War II it is quite clear that some 50 per cent of all dermatologic disability results from skin diseases which are classified in the broad group of dermatitis and eczema These diseases are characterized variously by erythema, vesiculation oozing crusting lichenification thickening and pigmentation of the skin The pathologic changes in the skin are quite characteristic though it is usually not possible to differentiate one type of chronic dermatitis from another histologically The principal and contributing factors in a particular case of dermatitis vary greatly In general, the longer the dermatitic inflammation of the skin has been present the greater the number of factors which may be contributory Such factors include (1) reactions to external contactants either as a primary cause or from treatment which has been applied (2) secondary infection acute or chronic, (3) excoriation from the itching which is almost an invariable symptom in dermatitis (4) blockage of sweat ducts which occurs to some degree after any dermatitis no matter how mild, (5) reactions to ingestants and inhalants (6) psychosomatic influences (7) peripheral vascular disease, (8) vasomotor disturbances

It is important to classify a particular case of dermatitis as accurately as possible and to determine the principal etiologic factor or factors before any consideration is given to the advisability of cortisone or corticotropin therapy At present it is our impression that these compounds are being widely overused and abused in the treatment of dermatitis

A bewildering array of terms has been applied to various types of acute and chronic dermatitis In an attempt to bring some slight order out of this terminologic chaos one [5] of us has recently prepared a classification in which the various types of dermatitis have been grouped under some nine main headings This is probably still more complex than might be desired but may be less confusing than the 100 to 150 terms containing the word *dermatitis* or *eczema* found in large textbooks of dermatology The indications for cortisone or corticotropin therapy will be considered in relation to the following types of dermatiti (1) acute contact dermatitis (2) atopic dermatitis (3) seborrheic dermatitis (4) eczematous contact type dermatitis (5) nummular dermatitis (6) lichen simplex chronicus, (7) chronic dermatitis of hands or feet (8) stasis dermatitis (9) miscellaneous dermatoses (including dermatitis directly or indirectly related to systemic disease, obscure erythrodermas chronic lichenoid and discoid dermatitis and lymphomas)

It is becoming apparent that in some instances of dermatitis hydrocortisone ointment either in the acetate or free alcohol form may equal or even surpass the effects of cortisone or corticotropin administered internally We have treated to date some 200 patients with the 2 5 per cent hydrocortisone ointment * Compared to the systemic administration of cortisone

* Acknowledgment is made to Merck and Co Inc and The Upjohn Company for supplies of hydrocortisone ointment used in this study

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To adults 200 to 300 mg of cortisone are given during the first 24 hours 150 to 200 during the second 24 hours, and 100 mg the third day Improvement is usually noted within 12 hours, almost always within 24 It is ordinarily not necessary to continue cortisone therapy for more than three days in a simple though severe, uncomplicated contact dermatitis Severe relapse after cessation of cortisone therapy is rarely encountered *unless exposure to the exciting agent is continued* There is rarely any necessity for corticotropin therapy in simple contact dermatitis cortisone by mouth is preferable

In a reaction of this type which is ordinarily self limited the advisability of instituting cortisone therapy might be questioned but we believe that it is justified in selected cases The discomfort in such dermatitis may be extreme and the external signs alarming There is always some risk of secondary infection, which may be severe It would seem quite certain that the short course of cortisone therapy which is necessary in such cases is far less dangerous than the administration of a specific antigen such as rhus extract Reactions to such specific antigen therapy during the acute phase of the eruption are frequently severe and may be fatal [26]

It has been established without question that cortisone therapy will be ineffective in contact dermatitis if there is continued exposure to the exciting agent The following case report is illustrative

A B male aged 40 was seen because of a severe contact dermatitis of the face apparently caused by camphor in a lotion which had been applied to the face The reaction was so extreme as to be disabling the eyes were swollen shut The patient was admitted to the hospital and 200 mg cortisone was given daily by mouth Although the conclusion that camphor was responsible for the dermatitis seemed fairly clear studies to rule out other possible agents and to determine other possible modes of exposure to camphor were undertaken The patient's wife was requested to bring in certain materials from the home one of which was a tin containing camphor that had been kept in a clothes closet In identifying this agent the patient was exposed to its vapors The momentary contact was sufficient to cause a complete relapse even though the patient at the time was receiving 100 mg of cortisone daily

This case demonstrates the importance of the principle that cortisone therapy is a stopgap in the treatment of contact dermatitis that it will be ineffective if exposure to the allergen continues and that control of the dermatitis will be dependent upon determination of the specific agent and prevention of reexposure to it In this connection, it must be kept in mind that patch testing during the acute phase of the dermatitis is highly inadvisable because it not only may cause a severe local reaction at the site of the patch test but may produce a complete relapse which may be more severe than the original attack of dermatitis Under any circumstances patch testing procedures should be done only by physicians who have had experience with the method are familiar with the proper concentration of the materials to be applied to the skin and are conversant with the inherent dangers of reexposure to any allergen A detailed history repeatedly reviewed is unquestionably of more value and less dangerous than extensive patch testing

When properly performed and interpreted patch tests often have considerable validity and usefulness though the conditions of application may not duplicate those encountered clinically in terms of friction maceration of the skin sweating and other factors Scratch or intradermal tests on the other hand are designed primarily to discover circulating allergens which produce the sensitization reaction chiefly in the deeper portions of the skin particularly in the blood vessels

It is apparently well established that the administration of cortisone does not significantly interfere with the patch test reaction Sulzberger et al [6] have determined the reactions to patch tests with serial dilutions of the allergen before and after administration of 150 mg of cortisone daily for three days and during application of the tests They found that there is a small but consistent trend toward diminution of the reaction at the sites of application of threshold concentrations of the allergen However in the case of allergens capable of producing fully developed or strong reactions to patch tests no interference with the response to standard concentrations could be discerned They conclude that patch tests during therapy are entirely feasible and have validity This is in accord with clinical experience as illustrated by the case report just cited

Although enough data to permit final conclusions have not yet been collected it would appear that hydrocortisone applied locally may become a useful method of treatment in contact dermatitis particularly if the process is fairly well localized A single report has been published in which a few patients with contact dermatitis were so treated [7] On the basis of our own experience to date it would seem that hydrocortisone ointment will be most effective in processes in which the integrity of the skin has been disturbed by vesiculation or scratching Our results would indicate that hydrocortisone ointment is not as effective as cortisone by mouth in contact dermatitis but is without any demonstrable hazard to date

Atopic Dermatitis This is one of the most characteristic syndromes in medicine In many cases it may be mild and just annoying but it is sometimes capable of producing total and prolonged disability

As the term *atopic* indicates the disease occurs in persons from allergic stock Ordinarily it is first seen during infancy and is the most intractable type of infantile eczema Itching is extreme and the eczematous involvement may be generalized Fortunately the infantile phase usually terminates spontaneously when the patient is about 2 years of age The dermatitis may persist continuously in some unfortunate children

After the usual infantile remission recurrence of the atopic dermatitis is ordinarily noted just before or during the teens At this time the distribution of the lesions is highly characteristic the face neck antecubital and popliteal spaces being the principal sites of involvement The disease may become almost completely generalized at times Atopic dermatitis is *commonly* accompanied by other allergic manifestations particularly asthma or hay fever It is a curious but frequent observation that often only *one shock* organ will be involved at a time e g during exacerbations of eczema the

patient may have no asthma or hay fever In some unfortunate patients, however, several organs may be shock sites at the same time Aside from rarely observed cataract or keratoconus and the late effects of rhinitis or asthma, the disease apparently is not accompanied by significant systemic disturbances Patients with atopic dermatitis are frequently of a rather distinctive personality type alert mildly hypomanic, usually quite intelligent and frequently afflicted with tensions and conflicts directed toward other members of the household often the patient's mother In addition chronic severe atopic dermatitis often produces profound effects upon the psyche because of disfigurement, loss of sleep and periodic unpredictable disability which interrupts the patient's social, scholastic, or occupational life

Atopic dermatitis is ordinarily better during the summer months except in very moist tropical weather Climatologic therapy may be extremely helpful even curative in some cases Fortunately the eventual outlook in at least 90 per cent of cases is toward almost complete subsidence of the dermatitis usually before the age of 25 In some patients in whom it persists, it may do so in the form of more localized dermatitis often on the hands Only occasionally does it persist unabated

Different types of atopic dermatitis have varying etiologic factors and these must be thoroughly considered in relation to the advisability or lack of advisability of cortisone or corticotropin therapy The following diagram indicates the principal factors involved in the perpetuation of atopic dermatitis and it will be immediately apparent that in some of these cortisone may have no beneficial effect

It is of interest to consider how cortisone might affect the various factors outlined in Figure 37 Psychomotor activity may be increased but ordinarily if the response to cortisone therapy is prompt in regard to itching and inflammation of the skin the sense of peace and freedom from symptoms experienced by the patient is striking This carries some danger of and by itself because such patients are often intolerant to and extremely depressed by the flare ups of the dermatitis which may accompany attempts to reduce the dose of cortisone They may be insistent that such therapy be continued at a dosage level which may produce undesired effects We have encountered patients who obtained further supplies of cortisone without authority

The itchiness and tickling skin which is so characteristic of patients with atopic dermatitis ordinarily is promptly relieved by cortisone therapy Since the changes seen in the skin are often largely the result of scratching relief of the itching is responsible for much of the objective improvement seen Sweat retention due to sweat duct blockage which is a constant finding in atopic dermatitis is not corrected structurally by cortisone therapy, but the miliaria (or prickly heat reaction) may be greatly reduced or completely suppressed In the presence of acute bacterial infection it obviously would be wisest to administer a suitable antibacterial agent though we have never observed extension of a superficial impetiginous or ulcerative infection of the skin as a result of cortisone or corticotropin therapy The effect of

cortisone upon antigen antibody reactions is not precisely determined, but *it certainly does not suppress them completely* If there is any element of reaction to applied contactants such as medication or cosmetics, cortisone will not suppress this as long as application is continued

A striking feature of atopic dermatitis is the susceptibility of the patient to infection of the skin with either herpes simplex or vaccinia virus and the explosive character of such infections

It is strongly advised that hormonal therapy be undertaken in atopic dermatitis only after the most careful consideration and after other methods of treatment have failed It is our policy to restrict such therapy to patients

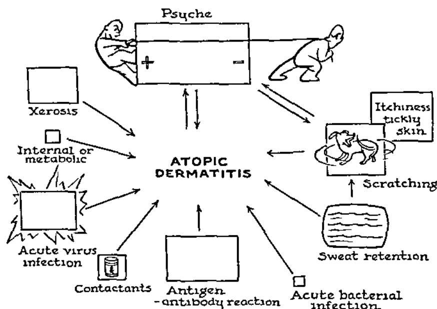


FIG 37 Etiologic factors in atopic dermatitis (From Pillsbury *Textbook of Dermatology* Philadelphia W B Saunders Company 1954)

whose dermatitis is extensive and productive of real disability It is also of the greatest importance that the patient understand fully that cortisone is not curative and that the eczema may recur in even more severe form after the therapy has been discontinued It is in such cases that the physician often finds himself caught on the horns of a dilemma of his own making

It is our policy almost invariably to insist that in patients with atopic dermatitis the effect of hospitalization be tried before cortisone is given Hospitalization alone often has strikingly good effects for reasons which are not fully clear at times In addition medical studies can be undertaken to determine whether or not any contraindication to hormonal therapy exists These should be done in the realization that it may be necessary to continue therapy for a rather long period of time

The initial dosage level which we employ is ordinarily 200 mg of corti

patient may have no asthma or hay fever In some unfortunate patients however, several organs may be shock sites at the same time Aside from rarely observed cataract or keratoconus and the late effects of rhinitis or asthma, the disease apparently is not accompanied by significant systemic disturbances Patients with atopic dermatitis are frequently of a rather distinctive personality type alert mildly hypomanic usually quite intelligent and frequently afflicted with tensions and conflicts directed toward other members of the household often the patient's mother In addition, chronic severe atopic dermatitis often produces profound effects upon the psyche because of disfigurement loss of sleep and periodic unpredictable disability which interrupts the patient s social, scholastic, or occupational life

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(1) Patients in whom the improved state of the skin is maintained consistently as the dose is reduced and who after some three or four weeks of therapy, may not have any significant flare up on complete cessation of treatment Unfortunately this group is small certainly not over 10 per cent of all patients in our experience

(2) In another group—probably the largest—reduction of the dose of cortisone will reveal a critical level which is needed to keep the condition under reasonable control Fortunately this dosage level (usually 25 to 75 mg daily) rarely causes any undesired effects Nevertheless every effort should be made to find a means of discontinuing cortisone entirely by the use of local therapy psychotherapy in selected cases or a change in environment if possible In some patients we have been able to terminate cortisone therapy by substituting corticotropin ordinarily in a slow absorption vehicle Here again the reduction in dosage must be cautious

(3) In a small group of patients probably between 10 and 20 per cent it is found that the 'critical' dose of cortisone is of the order of 100 to 200 mg This presents a very real and difficult problem which has made many physicians unwilling to institute hormonal therapy in atopic dermatitis If the eczema has been severe the patient frequently is anxious to continue therapy in rather high doses and is unwilling to accept the physician's reasons for the necessity of discontinuing it Moreover the flare ups of the dermatitis which may occur with attempts to reduce the dose often have a profoundly depressing effect which in itself may make the dermatitis worse As soon as it has been established that high doses will be necessary, it is believed advisable to make every effort to terminate hormonal therapy

Seborrheic Dermatitis Mild seborrheic dermatitis is a very common disease with characteristic moderate greasy scaling of the scalp on the sides of the nose and in the presternal and interscapular regions It is frequently associated with acne or with rosacea The basic mechanism involved is not known though there is obviously some disturbance of the surface fats of the skin Local treatment is reasonably satisfactory if regularly carried out, and cortisone or corticotropin therapy is *never* justified in patients with mild dermatitis

In some individuals seborrheic dermatiti may develop into an extremely extensive and disabling disease The bacteria encountered in normal skin flora are often completely replaced by pathogenic or potentially pathogenic bacteria Chronic low grade or recurrent acute superficial infections may be noted especially about the ears and in intertriginous areas such as the axillas under the breasts and the anogenital region In a warm environment severe and extensive miliaria is common and may be of the pustular variety It is quite apparent in these patients that blockage of a high percentage of the sweat ducts has occurred either uperficially or at lower levels in the skin and that they sweat into rather than onto the skin In such patients the disturbance of sweating may be sufficient to predispose the individual to so called tropical asthenia and to a much reduced efficiency in a warm environment

sone daily by mouth divided into four doses during the 24 hour period There is no advantage whatever—in fact it is usually disadvantageous—to awaken the patient to give the cortisone Since oral cortisone became available we have had no reason to administer the hormone parenterally for atopic dermatitis If this initial dosage is not productive of improvement which fortunately is uncommon we rarely try higher doses for we believe that further increase in the dosage is justified only in the most severe and extensive cases because of the possibility of undesired hormonal effects

In patients with atopic dermatitis we have deemed it advisable to determine the maintenance dose as soon as possible, but make every effort not to subject the patient to a severe rebound of the dermatitis Since the skin may be easily observed and increase of itching is a good warning signal of relapse inadequacy of the dose of cortisone usually is quickly apparent As a rule the dose of cortisone is maintained at a level of 200 mg daily for four days and is then reduced by 25 mg decrements every three or four days until a dosage level of 100 mg daily is reached This often approaches the critical level for control of the eczema in many patients From this point on, *no reduction in the daily dose greater than 12 5 mg is attempted* We have encountered numerous instances of patients in whom reduction of the dosage level by as much as 25 mg in any one day resulted in severe relapses which were controlled with difficulty

In at least half of the patients with atopic dermatitis it is possible to control the eczema satisfactorily with a daily dose of 25 to 75 mg In young persons—and patients with this disease are ordinarily young—we have as yet encountered no adverse effects from this dose even in those who have continued such treatment for several months to two years

It is worth while to make an effort to keep the patient on a dose of cortisone which will *almost but not quite control* the eczema completely Various local methods of treatment can then be tried Oftentimes fortunately with the coming of warmer spring weather the dermatitis may subside into a remission which will permit cessation of cortisone therapy

The following results have been observed in the treatment of atopic dermatitis with cortisone

In a significant percentage of patients probably about 25 per cent, the results of hormonal therapy will be disappointing the improvement varying from none to moderate This is ordinarily the case where the inflammatory changes are less acute such as in those patients with atopic dermatitis in whom the skin is very dry and the objective changes are produced largely by scratching Under such circumstances this failure in treatment will soon be apparent in most patients usually within three or four days after cortisone therapy is started The physician is then well advised to discontinue hormonal therapy as soon as possible and *not* to use larger doses i e , of the order of 300 to 400 mg daily

In acute severe flare ups of atopic dermatitis with marked inflammatory changes, the initial effect of cortisone therapy is ordinarily excellent The further course of such patients falls into three general groups

For these reasons we rarely advise cortisone or corticotropin in extensive eborrheic dermatitis If it is chosen it is essential that supplementary methods be used including appropriate antibiotic therapy and placing the patient in a cool environment Supplementary X ray therapy is recom mended by others but we have almost entirely discontinued the use of ordinary superficial X ray therapy in "benign" inflammatory diseases of the skin

The rebound of seborrheic dermatitis on discontinuance of cortisone therapy or even of gradual lowering of the dose may be more severe than the condition originally treated If cortisone therapy is continued for a prolonged period we believe that it is worth while indeed highly advisable to stimulate adrenocortical function by discontinuing cortisone and administering corticotropin in its place for two to three weeks Various types of topical therapy, if expertly selected may be extremely helpful in maintaining the improvement which has been accomplished with cortisone and in reducing the possibility of a rebound reaction It should be kept in mind that in extensive seborrheic dermatitis particularly in middle-aged patients a diabetic background may be present It is obviously essential to examine a patient for this initially and to keep it in mind during the entire course of hormonal therapy

Eczematous Contact type Dermatitis This disease which forms a large sector of the dermatitis group is constantly increasing by reason of the availability of more and more chemicals which are capable of sensitizing the human skin Most cases of chronic industrial dermatitis fall within this category For all practical purposes chronic fungus infections of the feet which become persistently inflammatory may be considered part of this group Many cases of chronic dermatitis induced by topical therapy by cosmetics and by household chemicals are included Other terms which have been attached to this condition are patchy eczematous dermatitis and chronic infectious eczematoid dermatitis '

Unless there is no reasonable chance of controlling the etiologic factors we are unwilling to use cortisone therapy in this condition It seems probable however that local hydrocortisone ointment may be justifiable and valuable particularly in patients in whom the dermatitis is not extensive

Nummular Dermatitis This is a form of dermatitis which is distinctive *morphologically though the etiologic factors are very poorly understood* It is seen principally in adults of middle to old age The lesions begin as circular patches of dermatitis (nummular or coin shaped) which are distributed initially on the extensor surface of the extremities and the back Nummular dermatitis may sometimes appear rather explosively in a patient who has had a patch of chronic dermatitis on one area of the body often the lower legs This has also been termed an id reaction and apparently is initiated by absorption of an unknown material from the primary site frequently following infection of the area or by a reaction to topical therapy Patches of nummular eczema often show evidence of bacterial infection which may be controlled though with difficulty with judicious local treatment Lowered

Case Report

Severe secondarily infected dermatitis partially controlled by cortisone or corticotropin therapy with "cure" with hydrocortisone ointment

The patient a male student aged 18 was first seen in August 1952 He was moderately overweight and gave a history of epileptic seizures which had started some years previously but had been controlled by Dilantin and Tridione The dermatitis had first appeared in the early part of 1952 with scaling erythematous lesions of the scalp sides of the nose and suprapubic region In spite of what seemed to be appropriate local therapy the dermatitis had gradually extended and marked secondary infection had occurred When the patient was first seen by us there was severe involvement of the scalp face axillas anogenital region and upper thighs with gross evidence of secondary bacterial infection The patient was almost completely disabled He was admitted to the hospital where he remained from August 16 to September 19 1952 After the usual preliminary studies including roentgenogram of the chest cortisone therapy was initiated in a dose of 200 mg daily Terramycin was also administered to control the secondary infection The initial improvement was marked but no further improvement was noted after about two weeks of therapy at the initial dosage level Cortisone was then discontinued and corticotropin gel 40 units daily was administered This produced further improvement and the patient was discharged from the hospital Corticotropin therapy was continued in a dose of 30 units of the gel preparation every third or fourth day Attempts to lower the amount of each dose or to increase the interval between injections immediately resulted in marked exacerbation of the dermatitis

During this period of treatment no epileptiform attacks were noted Because of the possibility that a drug sensitivity might be playing a role in the dermatitis the administration of Tridione and Dilantin was discontinued There was no improvement of the dermatitis but the patient experienced an epileptic seizure shortly thereafter Tridione and Dilantin therapy was resumed The dermatitis could be partially controlled by cortisone or corticotropin but was never completely suppressed

On January 31 1953 hydrocortisone (free alcohol) ointment (2 5 per cent) was dispensed along with a tube of placebo ointment The hydrocortisone ointment produced marked and very rapid improvement the placebo had no effect After two days of such therapy the patient insisted upon using the hydrocortisone ointment on both sides of the body Cortisone therapy by mouth was discontinued without resultant exacerbation With regular daily application of a small amount of hydrocortisone ointment to the involved sites the patient has remained in excellent condition for three months

In this patient, the local application of hydrocortisone ointment produced results which were definitely superior to those of either cortisone by mouth or corticotropin intramuscularly Whether or not this effect will continue remains to be seen

The temporary effects of cortisone or corticotropin therapy in extensive and severe seborrheic dermatitis are ordinarily very marked However it must be remembered that in extensive seborrheic dermatitis at least three significant disturbances have occurred in the skin, and these are ordinarily irreversible It is extremely difficult to bring the bacterial ecology back to normal There are no satisfactory means of relieving the sweat retention syndrome in the skin though this may be controlled very adequately by a cool environment It is likewise difficult, sometimes impossible to produce permanent correction of the abnormal fats of the skin surface and of the disturbance in the sebaceous glands

large, 100 to 150 mg daily being sufficient Gradual reduction in the dose over a period of two to three weeks is often possible along with adequate therapy to control the stasis and scrupulous avoidance of any topical medication which may be sensitizing Hydrocortisone ointment may be extremely helpful in controlling resistant patches of dermatitis

Miscellaneous Dermatoses Brief mention may be made of several other dermatoses in which some experience with cortisone therapy has been acquired One of the most important of these is psoriasis Some initial reports on treatment of chronic psoriasis have been favorable but the experience of other observers [28–30] including ourselves has not confirmed this As a rule no effect whatever can be observed in the patches or plaques of chronic psoriasis from cortisone therapy If there is any improvement whatever it promptly disappears following cessation of such treatment In ordinary chronic psoriasis therefore hormonal therapy is not advised

One exception to this statement is found in the severe exfoliative exacerbations of psoriasis particularly in patients with a concomitant arthritis [31] In such patients the erythema and scaling of the skin may affect all parts of the skin surface itching and burning may be extreme and there may be marked general symptoms by reason of excessive protein losses from exfoliation interference with temperature regulation because of the large volume of blood at the skin surface and interference with sweating In such patients the possibility of eventual development of some type of lymphoma must be kept in mind The condition may be extraordinarily chronic and completely disabling Various types of topical and internal therapy are usually ineffective In such patients cortisone or corticotropin therapy is distinctly worth a trial though the results are unpredictable In occasional patients partial rehabilitation may be possible

Urticaria Acute urticaria following ingestion of foods or drugs to which the patient is sensitive is of course one of the more common allergic states in which the skin may be affected Though the lesions may persist for days or weeks at times as they do after serum type reactions from penicillin the course of the urticarial outburst is usually short In mild cases a trial of antihistaminic therapy is the initial treatment of choice If however the urticaria is severe and persistent we would unhesitatingly administer cortisone provided there are no cogent contraindications Such treatment usually is rapidly effective It has seemed worth while in some patients to administer 200 mg of cortisone in a single initial dose and continue treatment for three or four days in a dosage of 200 to 300 mg every 24 hours In otherwise healthy individuals it has been our experience that this dosage method does not produce undesired effects The dose may be rapidly reduced thereafter by decrements of as much as 50 mg daily Since urticaria is ordinarily a self limited disease the condition ordinarily will not recur when cortisone therapy is terminated *provided the patient does not continue to receive the food or drug responsible*

Chronic Urticaria This condition is much less amenable to cortisone therapy in fact the results are so poor as to make such treatment hardly

humidity of the environment, particularly in overheated homes during the winter almost invariably makes a nummular dermatitis worse Exposure to sunlight is usually beneficial The disease may be recurrent every winter for several years Prolonged soap and water bathing is extremely harmful and older patients with nummular dermatitis must ordinarily revise their bathing habits drastically

Although cortisone therapy is ordinarily quite striking in its effect upon this disease it is not recommended because the condition is usually not disabling recurrences after cortisone therapy are often more severe than the original condition and judicious use of other methods of treatment is usually effective On the basis of experience to date it would appear that, if any hormonal therapy is to be employed hydrocortisone locally will be preferable to cortisone or corticotropin given systemically

Lichen Simplex Chronicus (Localized Neurodermatitis) In this condition the essential change is an area of tickly or itchy skin which the patient scratches repeatedly often unconsciously There is often a marked psychosomatic factor the patient responds to tension by scratching this area of skin Cortisone or corticotropin internally is not advised If there is oozing in the area or if the integrity of the skin is disturbed by scratching local hydrocortisone therapy may be very useful However in areas which are simply thickened and lichenified no effect from hydrocortisone may be noted Once the cycle of scratch itch scratch is broken spontaneous healing of the skin occurs However in some patients the dermatitis and itching may persist for many years The lesions may occur anywhere but the sites most frequently involved are the occipital area in women about the ankle knees or hands and in the perianal and vulvar skin

Chronic Dermatitis of Hands or Feet This is a very common dermatologic problem It often produces marked disability in members of the Armed Forces in industrial workers in physicians and nurses, and in house wives, particularly young mothers The etiologic factors involved are complex and numerous with vasomotor disturbances psychosomatic *hyperhidrosis* reactions to irritants and sensitizers and superficial fungus infections predominant In severe cases the condition frequently is chronic and sometimes impossible to arrest if the environment is not ideal in respect to exposure to irritants and sensitizers Systemic cortisone or corticotropin therapy is rarely advisable We have observed several patients in whom topical application of 2 5 per cent hydrocortisone ointment produced satisfactory control of the dermatitis

Stasis Dermatitis For the ordinary uncomplicated stasis dermatitis or ulcer it is obvious that cortisone therapy would represent a rather unphysiologic method of treatment However stasis dermatitis is sometimes complicated by local skin sensitization and by explosive and extensive id eruptions which may persist for long periods of time Such a disseminated dermatitis is not infrequently seen after the induction of a local sensitization reaction by topical medication If the dermatitis is severe and disabling the use of cortisone is often justified The initial dose required is usually not

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possible to lower the daily dose to 25 and 37.5 mg daily, respectively, with hair growth progressing at a normal rate

Some regrowth of hair was noted in 16 of the 22 patients treated with initial growth being observed in from three to six weeks. In no patient was regrowth complete. There was clear evidence that the outlook for regrowth was poor if the alopecia had had its onset prior to puberty and if the disease had been present for a very long period of time. Also regardless of other factors regrowth of axillary and pubic hair is unlikely following cortisone therapy.

In 7 of the patients reported by these authors the period of observation was sufficient to permit some evaluation of results from the cosmetic point of view and in 4 of these it was felt that reasonably satisfactory effects had been obtained. In one patient with trophic nail changes associated with a universal alopecia considerable improvement in nail growth was noted after three months of therapy. No severe undesired effects occurred but the mild ones which were noted demonstrate the importance of adequate regular observation of patients receiving rather prolonged cortisone therapy.

Unfortunately there was a marked tendency to relapse to the original condition of alopecia on cessation of cortisone therapy. Growth could be induced again in such cases by reinstituting the hormone. The authors conclude that the mechanism whereby cortisone causes stimulation of hair growth is still obscure and theorize that it may act "by change in local chemical milieu through some such manner as influencing sebaceous gland function or keratinization." We are in complete agreement with Dillaha and Rothman that this form of therapy is not to be recommended for general use in the treatment of alopecia areata. It is a good example of the use of 16 inch guns to shoot sparrows.

Topical Therapy with Hydrocortisone Ointment

Topical cortisone acetate therapy in diseases of the skin has not been proved to be of value.[17] This is in contradistinction to the effectiveness of cortisone suspension or ointments in the eye and possibly at the mucocutaneous junction of various body orifices.

Although the only fairly extended study on the use of hydrocortisone ointment is that of Sulzberger, Witten and Smith[27] their data indicate clearly that hydrocortisone ointment may be of marked value in certain types of skin diseases and may make it unnecessary to give cortisone systemically in a considerable proportion of patients suffering from benign inflammatory reactions of the skin. Our own experience with hydrocortisone ointment is relatively brief but some 200 patients with various types of dermatoses have been treated. In certain types of inflamed oozing dermatitis, the effects of hydrocortisone ointment may be so rapid as to be startling exceeding even the effects of cortisone given systemically. To date no untoward effects whatever of such therapy have been seen but further investigation will obviously be necessary before final conclusions can be made

worth while Our experience has been similar to that of Sulzberger and his associates[6] in that, rather surprisingly the appearance of urticarial lesions is not suppressed by cortisone to any appreciable extent in a considerable proportion of patients Furthermore rapid recurrence is noted on cessation of therapy Chronic urticaria is an extremely difficult disease to treat successfully This is especially true if dermographism is present Skin tests with foods are probably worthless in this condition Evidences of general illness, with the possible exception of occasional foci of infection and psychosomatic factors, usually are not present Antihistaminics regularly administered may be effective though tolerance to them often is acquired eventually The passage of time and a beneficent regimen in respect to nervous tension and physical activity seem to be the most effective methods

Alopecia Areata The observation that administration of cortisone will cause temporary regrowth of hair in patients with alopecia areata is of interest as a possible means of better understanding of the physiology of hair growth and of the effects of cortisone upon a particular organ system However hormonal therapy is not recommended because (1) the effects are unsatisfactory in many patients from the standpoint of complete regrowth, (2) regrowth of hair is temporary and continued administration of cortisone is necessary to maintain it and (3) for the temporary amelioration of a disease having only cosmetic significance, administration of a compound capable of producing undesired effects as a result of overdosage is not warranted

The following summary of the effects of cortisone in alopecia areata is taken principally from the excellent article by Dillaha and Rothman[3] Walker and Rothman[33] had previously studied 230 patients in an effort to determine whether there were any consistent underlying abnormalities in this disease, with particular reference to endocrine disease They concluded that there is no regular evidence of endocrine abnormality However their studies clearly showed that alopecia areata tends to be more severe when it has its onset before puberty, that pregnancy and lactation sometimes have a markedly beneficial effect upon alopecia totalis and that *occasionally* thyrotoxicosis and alopecia areata begin simultaneously

The report of Dillaha and Rothman[3] is concerned with the effect of orally administered cortisone in 22 patients 11 of whom had alopecia which was nearly universal In 16 of the patients the alopecia seemed relatively stationary at the time treatment was instituted and in 5 others it was showing extension The duration of the reported attack of alopecia areata varied from 3 months to 20 years the average being over 6 years After preliminary physical and laboratory examinations the patients were given cortisone by mouth in an initial dose of 100 to 150 mg daily which was continued for four weeks or longer In patients in whom early hair regrowth was noted the dose was gradually lowered in an attempt to establish the minimum maintenance dose which would promote active hair growth It was found that an initial dose of at least 100 mg a day was necessary In 2 patients it was

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The following summary is based principally on the report of Sulzberger, Witten and Smith [7] Experimental demonstration of the probable effect of hydrocortisone locally upon the skin was available from the report of Goldman, Preston, and Rockwell [10] who showed that reactions to application of contactant allergens on the skin could be prevented by the intradermal injection of a hydrocortisone acetate suspension They noted that this zone of inhibition of the reaction extended beyond the immediate site of injection

Sulzberger and his associates used ointments containing hydrocortisone in concentrations of 1 2 5 and 5 per cent respectively in various bases They believe that the 5 per cent ointment is superior to the 2 5 per cent, and the 2 5 per cent a little superior to the 1 per cent However these differences were apparently not marked enough to make any final conclusions, and continued experimental and clinical study of the effect of various concentrations is necessary Reduction of the hydrocortisone content to the lowest effective concentration is of importance from the economic standpoint because of the present cost of compound F From our own experience, it would appear that an extremely thin layer of ointment applied to the skin is as effective as larger amounts To date, the effectiveness of one ointment vehicle over another seems not to have been demonstrated at least in the experience of the Sulzberger group

The largest group of patients 30 in all, treated by Sulzberger Witten, and Smith had atopic dermatitis Eminently satisfactory" results were noted in 20 of these Our own experience though less extensive has been similar Of 10 patients with atopic dermatitis on whom adequate follow up reports were available satisfactory results were noted in 8 In 2 patients, both of whom had very dry lichenified skin without acute inflammation or exudation the hydrocortisone ointment showed no superiority over the placebo

In 5 patients with vulvar and/or anal pruritus the Sulzberger group obtained good results in 3 Our experience with this difficult dermatologic condition has been even more encouraging In 7 of 8 patients treated for long standing anal pruritus the results have been extremely satisfactory, and the rapid subsidence of itching is often striking Our study has not been continued long enough to determine the permanence of results Many cases of anal pruritus are perpetuated by the scratch itch scratch cycle and are essentially a localized neurodermatitis if significant remission of the itching can be produced the cycle may be interrupted for prolonged periods

Sulzberger Witten and Smith state that "in several cases lichen chronicus simplex nummular eczema and distinctive exudative discoid and lichenoid chronic dermatosis were also improved to some degree" We have treated only 1 case of the latter condition, with indifferent results The experience with hydrocortisone in lichen simplex chronicus in our own series has been mixed as to effectiveness of the hormone but in general it appears that unless the integrity of the skin is disturbed as in an oozing and exudative patch the results are less likely to be favorable In such patients, moreover the ointment may tend to lose its effectiveness as the acute manifestations subside A similar finding has been noted in nummular eczema or dermatitis

Table [illegible]

EVALUATION OF ADRENOCORTICAL THERAPY IN SELECTED SKIN DISEASES

Disease or Syndrome	*Effect of Cortisone or Corticotropin Therapy*	*Justification for Use*
Angioneurotic edema	Very effective	In severe cases particularly if there is risk of laryngeal involvement
Contact dermatitis	Very effective	Systemic cortisone therapy justified only in very severe and extensive involvement Hydrocortisone ointment preferable and possibly the most effective treatment in localized less severe cases
Dermatitis medicamentosa	Effectiveness varies depending upon type of eruption	Fully justified in severe cases particularly if internal organs as well as skin are shock sites of the reaction
Atopic dermatitis	Variable but morbidistatic in probably 75% of cases	*Only* in carefully selected patients with extensive disabling involvement Prolonged therapy often necessary *Not* to be used in mild to moderate forms
Exfoliative dermatitis	Variable particularly effective in allergic dermatitis	Almost always indicated in severe extensive involvement though necessary therapy may be prolonged
Seborrheic dermatitis	Highly effective	Careful consideration necessary Justified only in severe extensive involvement not controlled by other methods of treatment Hydrocortisone ointment may be preferable in some patients
Pemphigus	Regularly effective though very high doses usually necessary	Always justified and indicated unless some very compelling contraindication to hormonal therapy exists
Nummular dermatitis	Almost always effective	Variable usually not justified Reserve for extensive severe involvement with realization that prolonged therapy or repeated courses may be necessary

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Table 26—(Continued)

Disease or Syndrome	*Effect of Cortisone or Corticotropin Therapy*	*Justification for Use*
Erythema multiforme (all types)	Only effective method of treatment	Always justified in severe cases provided no contraindication exists Occasionally though not commonly prolonged therapy necessary
Id eruptions	Almost always effective	Severe cases only
Erythema nodosum	Almost always effective	Variable depending upon severity Careful study to determine whether lesions are part of invasive phase of infection such as tuberculosis or coccidioidomycosis Great caution advisable
Visceral lupus erythematosus (acute disseminated lupus erythematosus)	Almost always morbidistatic high doses and prolonged therapy frequently necessary	For control of acute exacerbations probably not advisable in low grade manifestations
Cutaneous lupus erythematosus (chronic discoid)	Uncertain and variable	Not recommended Chloroquine or atabrine effective Gold salts *not* recommended
Psoriasis	Only occasionally effective particularly in extensive involvement of skin with arthritis	Only severe cases Not indicated in ordinary chronic psoriasis
Sarcoidosis	Variable and uncertain	Rarely to sometimes indicated
Mycosis fungoides	Extremely variable other methods such as X ray have more regular effect	Rarely
Chronic anal and vulvar pruritus	Systemic administration variably effective	Systemic therapy justified only in cases with secondary contact dermatitis Hydrocortisone ointment apparently superior often strikingly so
Lichen planus	Rarely effective	Not recommended
Alopecia areata	Quite effective in producing temporary partial regrowth of hair	Not justified
Post herpetic neuralgia	Uncertain	Preliminary trial of other methods preferable
Lepra reaction	Evidence of some effectiveness accumulating	Dependent upon judgment of physician experienced in treating leprosy
Dermatomyositis	Rarely effective	Probably always worthy of trial
Dermatitis herpetiformis	Rarely effective	Not recommended
Keloids	Doubtful	Not recommended
Chronic urticaria	Most uncertain Permanently good results uncommon	Not recommended

Sulzberger and his associates found hydrocortisone ointment of no effect in the treatment of psoriasis chronic discoid lupus erythematosus pemphigus vulgaris, and alopecia areata Our experience is similar with respect to psoriasis In carefully controlled clinical experiments in which similar symmetric lesions could be treated with the ointment and a placebo no difference was demonstrable

These authors noted that in their patients the effect of the ointment seemed to disappear some four or five days after discontinuance of application We have not yet had sufficient opportunity to determine this but it would seem that in many patients the occasional application of the ointment even as infrequently as every two or three days may be adequate to keep the process under control Fortunately moreover if an area of skin can be kept more normal for a fairly long period of time secondary factors such as injury from excoriation secondary infection and miliaria may be overcome to a considerable extent

Summary

To complete this essay of adrenocortical therapy in skin conditions it is pertinent to mention that the preferred methods of attaining optimum and maintenance dosages are the same as those established for rheumatoid arthritis (*q v*) and allied disorders Similarly the same rules regarding duration of therapy, avoidance of undesired effects and gradual stepwise reduction of dosage to preclude rebound reactions are in order Conditions constituting contraindications to therapy are discussed at length in other chapters of this volume

In this résumé of the effects of cortisone and corticotropin upon various diseases affecting the skin certain conditions in which skin involvement occurs as part of a general systemic disease have not been considered These are fully discussed in other chapters In conclusion we refer to the tabulation in Table 26 of our own evaluation of cortisone or corticotropin therapy in selected skin diseases which indicates first whether or not such therapy is effective in controlling the disease and second whether or not we believe its use is justified in that particular disease

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Table 26—(Continued)

Disease or Syndrome	*Effect of Cortisone or Corticotropin Therapy*	*Justification for Use*
Erythema multiforme (all types)	Only effective method of treatment	Always justified in severe cases provided no contraindication exists Occasionally though not commonly prolonged therapy necessary
Id eruptions	Almost always effective	Severe cases only
Erythema nodosum	Almost always effective	Variable depending upon severity Careful study to determine whether lesions are part of invasive phase of infection such as tuberculosis or coccidioidomycosis Great caution advisable
Visceral lupus erythematosus (acute disseminated lupus erythematosus)	Almost always morbidistatic high doses and prolonged therapy frequently necessary	For control of acute exacerbations probably not advisable in low grade manifestations
Cutaneous lupus erythematosus (chronic discoid)	Uncertain and variable	Not recommended Chloroquine or atabrine effective Gold salts *not* recommended
Psoriasis	Only occasionally effective particularly in extensive involvement of skin with arthritis	Only severe cases Not indicated in ordinary chronic psoriasis
Sarcoidosis	Variable and uncertain	Rarely to sometimes indicated
Mycosis fungoides	Extremely variable other methods such as X ray have more regular effect	Rarely
Chronic anal and vulvar pruritus	Systemic administration variably effective	Systemic therapy justified only in cases with secondary contact dermatitis Hydrocortisone ointment apparently superior often strikingly so
Lichen planus	Rarely effective	Not recommended
Alopecia areata	Quite effective in producing temporary partial regrowth of hair	Not justified
Post herpetic neuralgia	Uncertain	Preliminary trial of other methods preferable
Lepra reaction	Evidence of some effectiveness accumulating	Dependent upon judgment of physician experienced in treating leprosy
Dermatomyositis	Rarely effective	Probably always worthy of trial
Dermatitis herpetiformis	Rarely effective	Not recommended
Keloids	Doubtful	Not recommended
Chronic urticaria	Most uncertain Permanently good results uncommon	Not recommended

9

Granulomas Pulmonary Granulomatoses, Pulmonary Fibrosis, Other Pulmonary Conditions

Dickinson W Richards and John H McClement

In the field of pulmonary disease cortisone and corticotropin have been found to produce three general types of reaction (1) relief of asthmatic attacks in bronchial asthma and the asthmatic aspects of various chronic pulmonary conditions (2) subsidence of the acute inflammatory response to pulmonary infections sometimes with spread of the underlying infectious process (3) a variable symptomatic improvement in granulomatous and fibrogranulomatous states with greater or less degree of resolution of the disease

Although considerable work has been done knowledge of granulomatous and fibrogranulomatous conditions is still incomplete This group of diseases for one thing is heterogeneous and poorly defined containing many diverse entities Furthermore the effects of cortisone and of corticotropin have been irregular and unpredictable even in well-established pathologic conditions such as beryllioses or sarcoidosis While there has been some tendency toward better therapeutic response in the more acute cellularly active and recently developed cases it has not been consistent Analysis of the anatomic changes produced by cortisone or corticotropin has been hampered by the difficulty and hazard of repeated lung biopsy

This chapter is devoted to a review of the status of cortisone and corticotropin therapy in the major divisions of nonobstructive or nonasthmatic, granulomatous and fibrotic pulmonary diseases Other aspects of the chronic granulomatous diseases—cutaneous ophthalmologic visceral—are taken up elsewhere in this volume Brief reference is also made in this chapter to

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various other pulmonary conditions in which cortisone and corticotropin have been used

Sarcoidosis

Clinical pathologic, and physiologic studies have shown that among cases of pulmonary sarcoidosis there may be wide variation in the clinical manifestations, physiologic patterns of pulmonary dysfunction the natural course of the disease, and the histologic characteristics of the lesions An understanding of these variations among untreated cases is important in any consideration of the results of hormonal therapy and may help to explain some of the differences in results which have been observed Three types have been identified

Type I—Simple Restrictive Ventilatory Insufficiency In this group the lesions whether localized or diffuse, are largely interstitial and symptomatology is benign chiefly mild to moderate exertional dyspnea Physiologic study[1,2] shows (1) slightly reduced lung volume and ventilatory capacity, without emphysema (2) moderate hyperventilation at rest and during exercise, (3) normal arterial oxygen saturation and oxygen diffusing capacity (4) sometimes a moderate pulmonary arterial hypertension The clinical course is mild but usually prolonged

Type II—Syndrome of Diffusion Insufficiency or "Alveolar-Capillary Block" The clinical symptomatology in this group which has been described by McClement et al and Austrian et al [3] is apt to be progressive and severe (1) marked hyperpnea and tachypnea leading to increasing dyspnea (2) cyanosis on exercise later also at rest (3) persistent short nonproductive cough (4) sometimes clubbing of fingers and periods of fever (5) in fatal cases the terminal episode may be bronchopneumonia or right ventricular failure

The characteristic physiologic abnormalities are (1) reduction in lung volumes without evidence of emphysema (2) well maintained maximum breathing capacity (3) marked hyperventilation at rest and after exercise (4) normal or only slightly reduced arterial oxygen saturation at rest, with a marked fall on exercise (5) reduction in the oxygen diffusing capacity (6) disturbance in the pulmonary ventilation perfusion relationships (7) pulmonary arterial hypertension It is believed that the most important defect is the reduction in the oxygen diffusing capacity *Pathologically* diffuse involvement of the alveolar capillary septa is always found

Type III—Physiologic Findings of Chronic Pulmonary Emphysema Coates and Comroe[4] as well as Lukas[5] have found physiologic changes characteristic of pulmonary emphysema in a few patients with pulmonary sarcoidosis These studies and others have shown that all of the functional and hemodynamic changes seen in chronic pulmonary emphysema may be encountered though obstructive or asthmatic symptoms may be only slight Clinically the pulmonary insufficiency observed among this group has varied from mild to very severe and in some of these patients there was evidence that their disease had existed for a considerable period

Pathologic studies[6,7,8] have demonstrated that in the lung the sarcoid lesion may vary in location, extent and histologic characteristics. The extent may range from discrete miliary-like granulomas scattered throughout the lung with abundant areas of normal lung between the nodules to massive involvement with nearly all the alveolar capillary septa infiltrated with an almost continuous granulomatous process. The amount of fibrous tissue which is present in the granulomatous lesion varies greatly and this may be related to the age of the lesion. All variations have been seen from areas which contain little or no fibrous tissue to those with extensive fibrosis and hyalinization in which only small islands of typical granulomatous tissue still remain. In the lung the granulomas may be located in the alveolar capillary septa, in the pulmonary interstitium outside this septal area, about the blood vessels or even in the bronchi.

Hormonal Therapy

In the first reported use of adrenocortical therapy in a proven case of Boeck's sarcoid, Thorn and his group[9] observed that the administration of corticotropin (10 units per day for eight days) to a patient whose disease had been present for at least two years failed to produce any change in symptoms or in the lesions in the lungs, uveal tract or phalanges. There was evidence of adequate adrenal stimulation in this case.

The numerous clinical and clinicopathologic studies which followed this initial report have demonstrated the variety of responses that may be obtained when sarcoidosis is treated with these drugs. Engleman and his associates[10] as well as Straus[11] and Michael[12] reported their clinical and pathologic studies of cortisone-treated patients with lung or lymph node involvement. In these an increased sense of well being appeared, dyspnea decreased or disappeared if it had been present, pulmonary infiltrations cleared, enlarged peripheral lymph nodes became normal in size, serial biopsies of lymph node lesions showed the development of a more fibrous and less granulomatous reaction and in some the elevated serum globulin level decreased to normal. All of these changes appeared within three or four weeks of treatment. When treatment was discontinued, relapse to a pretreatment status appeared within three or four weeks in some but not all instances.

Subsequent reports[13-18] have confirmed these early observations. In a study of 13 patients with sarcoidosis Siltzbach[18] reported detailed observations on many of the clinical and pathologic results of treatment. He noted that some subjective improvement had occurred in every case but that in none had this improvement approached a cure. In 5 of 7 patients with severe disability there was however significant relief. Response to treatment was irregular and often transitory; lesions might regress in one area and remain stationary in another. He believed that new lesions were more amenable to treatment than old ones, although some which were known to be old regressed with treatment. Relapse occurred in 7 of 10 patients whose treatment had been stopped, and this relapse occurred as early as two weeks

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the granulomatous lesion of Boeck's sarcoid toward a more fibrous and hyalinized phase There may be a decrease in the constitutional and local manifestations of the disease with clearing of the chest X ray and a decrease in the size of lymph nodes liver spleen and other involved organs Physiologic improvement demonstrable by functional tests may sometimes accompany these gross changes However the degree of improvement varies widely from patient to patient The e variations in response can possibly be attributed to the duration extent location or histologic characteristics of the pretreatment lesion Relap e to pretreatment status occurs in a large number of patients within a short time after therapy is stopped

Dosage While the place of cortisone and corticotropin in the treatment of sarcoido is is not settled hormonal therapy should certainly be given a thorough trial in all cases of progressive di ease with symptoms

It is best in most cases to start with vigorous dosage, 200 to 300 mg of cortisone on the first day then 200 mg a day for one to four days then 100 mg a day until improvement is well under way which may take a week or even two or three weeks As soon as po ible the do age is lowered and an effort made to reduce the daily maintenance dose to 50 mg a day After symptoms and signs have reached a minimum plateau level a period without medication may be tried under clo e observation

Patients who do not begin to respond to this do age schedule within a few days may be given a trial with higher doses for a week or more as tolerated but not much can be expected in most resistant cases of this kind

Beryllium Granulomatosis

Corti one and corticotropin are as yet the only known agents having a definitive action in arresting and in some cases apparently resolving the manifestations of chronic beryllium poisoning

First recognized about twenty years ago[23] the damaging effects of exposure to beryllium and its salts have been extensively investigated Both acute and chronic progressive forms are recognized

There is an aceneform skin eruption which clears upon removal of the actual exposure An acute diffuse inflammation of the respiratory tract, caused by inhalation of fumes or dust containing beryllium or its salts is usually mild in nature and clears spontaneously without sequelae

The important and serious toxic manifestation however is a diffuse pulmonary granulomatosis caused by inhalation of beryllium particles It may develop following only slight exposure or occasionally after a long latent period The typical le ion is a small granuloma with central giant cell and peripheral epithelioid elements tending over months or years to progress to a chronic fibrosis The disease is in the lung parenchyma with interstitial infiltration causing loss of pulmonary expansion and characteristically a widespread thickening of alveolar septa As first shown by Wright Filley and Grinnel[24] the physiologic dysfunction is an alveolar capillary block similar to that described under Sarcoidosis Type II

Symptoms are dyspnea hyperpnea cyanosis and cough Van Ord

or as late as three months after cessation of treatment In 7 of 8 cases where serial biopsies were taken from Nickerson Kveim papules or sarcoid lesions of skin, lymph node, lung, or bronchial wall there was a discernible increase of fibrosis or hyalinization when the post treatment biopsy specimens were compared with pretreatment specimens In the 1 case in which no change could be detected the pretreatment lesion was described as already showing marked fibrosis and hyalinization

In addition to these clinical and pathologic studies a few reports of the effects of the hormones upon cardiopulmonary function in pulmonary sarcoidosis are available Galdston and his associates[19] studied a patient with pulmonary involvement and physiologic findings similar to those described under Type I During treatment they observed a slight increase in the lung volume and maximum breathing capacity The ventilation of the physiologic dead space decreased to normal but hyperventilation persisted Renold and others [0] in a study of the effects of smaller doses of corticotropin given by prolonged intravenous infusion found that a patient with pulmonary sarcoidosis obtained marked clinical improvement as well as a pronounced increase in the vital capacity, maximum breathing capacity, and arterial oxygen saturation Increase in the vital and maximum breathing capacities was also noted by Small [1] In a patient with pulmonary sarcoidosis and physiologic findings of chronic pulmonary emphysema i e Type III Lukas[2] observed that a reduction in cough, wheezing and dyspnea occurred after cortisone therapy was started and that the ratio of residual volume to total capacity decreased the vital and maximum breathing capacities increased and the arterial oxygen saturation at rest and during exercise returned to normal In this case many of the changes probably resulted from the relief of bronchial or bronchiolar obstruction McClement and his associates[2] found that in patients with the alveolar capillary block pattern (Type II), the response to cortisone was variable Two such patients had marked clinical improvement with an increase in lung volume, decrease in hyperventilation and return to normal of all the following measurements arterial oxygen saturation after exercise oxygen-diffusing capacity percentage of venous admixture in the arterial blood and pulmonary arterial pressure during exercise However, in 2 other patients whose disease was of longer standing, no significant change was observed in the physiologic findings during treatment In another patient with sarcoid and physiologic findings of chronic pulmonary emphysema (Type III), they observed an improvement in pulmonary function which was manifested chiefly by improved oxygenation of the arterial blood However in this case the characteristic lung volume changes of pulmonary emphysema and the previously observed pulmonary arterial hypertension could not be significantly altered by treatment They believed that this failure of some patients to make an adequate physiologic response could result either from the production of severe pulmonary fibrosis by treatment or from the fact that the lesion already was chiefly fibrotic before treatment was started

To summarize cortisone and corticotropin usually induce a change in

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To summarize, cortisone and corticotropin usually induce a change in

To summarize, experience with these agents in pulmonary granulomatosis due to beryllium is still fragmentary. It is sufficient, however, to provide a general guide to therapy as well as to prognosis, especially since the response in this disease appears to be similar to that in other chronic pulmonary granulomatoses.

Dosage In most instances substantial dosage is needed to affect the granulomatous lesion of berylliosis. Van Ordstrand[31] who has had perhaps the largest clinical experience with this disease, recommends that either cortisone or corticotropin be given in maximum dosage, i.e., cortisone in the range of 100 to 200 mg daily for several weeks followed by gradual reduction to maintenance levels. The effects produced by cortisone or by corticotropin in comparable dosage are essentially the same in most cases. Physiologic criteria of improvement are a rise in arterial oxygen saturation and a decrease in hyperpnea.

The response from patient to patient is so variable and unpredictable that treatment should be individualized. Improvement in some patients will begin within a few days, in others within a month or occasionally two months. Since dosage is high, unfavorable side effects have to be watched for constantly. In many instances the maintenance dosage represents a balance between the amount of improvement that can be achieved and the patient's tolerance. Sometimes, however, remarkable control of symptoms is obtained and only small maintenance doses of 50 or 25 mg of cortisone daily are needed. Intermittent courses of cortisone therapy may suffice; occasionally the drug can be discontinued altogether without return of symptoms.

Pulmonary Aspects of Collagen Diseases

Diffuse Scleroderma Because of the effects which cortisone and corticotropin have been demonstrated to have in some of the other diseases of collagen, it is not surprising that these agents have been used in cases of diffuse scleroderma with pulmonary involvement.

Clinically, patients with scleroderma involving the lungs have dyspnea which is often only slowly progressive but which eventually may become extremely severe and complicated by right ventricular failure. A nonproductive irritative cough is another frequent complaint. Baldwin, Cournand and Richards[1] as well as Austrian et al.[3] have shown that these cases have a physiologic pattern similar to that described under Sarcoidosis Type II, i.e., alveolar capillary block. Studies of autopsy material[3-34] have shown that late in the course of this disease the principal pulmonary finding is a hyalinized and fibrous organization of the pleura, alveolar capillary septa and the pulmonary interstitial tissue. This process leads to the formation of cystic areas as well as dense zones of fibrous tissue. In addition, the alveolar septa and the bronchial walls may be infiltrated by inflammatory cells, and one author[34] has described adenomalike proliferations about the small bronchi and bronchioles. Some ectasia of the small bronchi has been frequently observed.

strand,[4] who has followed a large number of patients with this disease, reports that one third of his series have died, one third have shown progressive deterioration, and in one third the clinical condition has been more or less stationary

Against this background experience in treatment of pulmonary berylliosis with cortisone and corticotropin over the past two or three years has shown that these agents in most instances produce some amelioration in the disease but that this effect is extremely variable extending from complete relief of symptoms in some patients to little or no improvement in others Wright[5] reported a case in which cortisone was continued for 134 days in dosages varying from 33 to 100 mg daily The patient's clinical condition previously deteriorating began to improve and pulmonary function and work tolerance increased throughout the period of treatment Kline Inkley and Pritchard[6] reported 5 patients with chronic berylliosis who were treated with corticotropin and cortisone Four were started on 100 units of corticotropin daily, continued at this level for one week, and then reduced gradually to a maintenance dose of 20 units daily Cough and dyspnea improved X-rays showed partial clearing The improvement persisted for a short time after treatment was discontinued One patient had a recurrence two months later with favorable response to a second course of treatment Another developed symptoms with the onset of pregnancy and improved only after the dosage of corticotropin was increased progressively for two months eventually reaching 100 units daily Cortisone in a dosage of 150 mg daily was then substituted and after 87 days the patient was delivered of a normal infant who developed a transient glycosuria after birth but recovered

De Nardi[7] reported 2 patients 1 treated successfully with corticotropin and a second who failed to improve with cortisone, 150 mg a day for 12 days but later did so on corticotropin This patient was maintained on 20 units of corticotropin daily Ferris et al,[8] in describing a series of patients treated with cortisone and corticotropin mentioned 3 with beryllium granulomatosis All improved with corticotropin in doses ranging from 25 to 160 units daily

One case of berylliosis successfully treated with cortisone is included in the large general experience reported by Krupp et al[9] In the series of Kennedy et al[10] who gave corticotropin in doses of 100 units a day there were 2 patients with berylliosis In 1, treatment had to be discontinued after 28 days because of emotional instability but physical improvement continued for two months thereafter The other patient received treatment in three separate courses, and his improvement also continued for several weeks after the last course

Austrian et al[3] reported 1 case of probable berylliosis in which no improvement was obtained after four weeks of cortisone, 100 mg daily Pulmonary function studies showed no change from pretreatment values Clinically it appeared that the disease process was gradually progressing unfavorably

To summarize experience with these agents in pulmonary granulomatosis due to beryllium is still fragmentary It is sufficient, however to provide a general guide to therapy as well as to prognosis especially since the response in this disease appears to be similar to that in other chronic pulmonary granulomatoses

Dosage In most instances substantial dosage is needed to affect the granulomatous lesion of berylliosis Van Ordstrand[31] who has had perhaps the largest clinical experience with this disease, recommends that either cortisone or corticotropin be given in maximum dosage i e, cortisone in the range of 100 to 200 mg daily for several weeks followed by gradual reduction to maintenance levels The effects produced by cortisone or by corticotropin in comparable dosage are essentially the same in most cases Physiologic criteria of improvement are a rise in arterial oxygen saturation and a decrease in hyperpnea

The response from patient to patient is so variable and unpredictable that treatment should be individualized Improvement in some patients will begin within a few days in others within a month or occasionally two months Since dosage is high unfavorable side effects have to be watched for constantly In many instances the maintenance dosage represents a balance between the amount of improvement that can be achieved and the patient's tolerance Sometimes however remarkable control of symptoms is obtained and only small maintenance doses of 50 or 25 mg of cortisone daily are needed Intermittent courses of cortisone therapy may suffice occasionally the drug can be discontinued altogether without return of symptoms

Pulmonary Aspects of Collagen Diseases

Diffuse Scleroderma Because of the effects which cortisone and corticotropin have been demonstrated to have in some of the other diseases of collagen, it is not surprising that these agents have been used in cases of diffuse scleroderma with pulmonary involvement

Clinically patients with scleroderma involving the lungs have dyspnea which is often only slowly progressive but which eventually may become extremely severe and complicated by right ventricular failure A nonproductive irritative cough is another frequent complaint Baldwin Cournand and Richards[1] as well as Austrian et al[3] have shown that these cases have a physiologic pattern similar to that described under Sarcoidosis Type II i e alveolar capillary block Studies of autopsy material[32–34] have shown that late in the course of this disease the principal pulmonary finding is a hyalinized and fibrous organization of the pleura alveolar capillary septa, and the pulmonary interstitial tissue This process leads to the formation of cystic areas as well as dense zones of fibrous tissue In addition the alveolar septa and the bronchial walls may be infiltrated by inflammatory cells and one author[33] has described adenomalike proliferations about the small bronchi and bronchioles Some ectasia of the small bronchi has been frequently observed

Most of the patients with scleroderma whose treatment with cortisone or corticotropin has been reported either have not had significant pulmonary disease, or they have been studied by investigators who were principally concerned with some other aspect of the disease. In the group of patients with scleroderma reported by Bayles et al [35] there is one who apparently had involvement of the lung. During treatment with corticotropin (40 units daily for 20 days) moderate improvement occurred in the skin and joint manifestations but no change in her pulmonary status is mentioned. West and his associates[36] summarized the treatment with cortisone of a patient with generalized scleroderma and pulmonary involvement: 100 mg was given daily for 15 days followed by 150 mg daily for 4 days. The pulmonary symptoms were not altered and repeated cardiopulmonary function studies showed an unchanging pattern of alveolar capillary block. During this period the involved skin improved slightly. Taubenhaus and Lev[37] observed that the cough subsided and breathing became easier in a patient with scleroderma involving the lungs during treatment with cortisone (300 and 200 mg on the first and second days followed by 100 mg daily). There was no change in the appearance of the chest X ray during treatment but the skin and joint manifestations improved and skin biopsies showed some loosening of the collagen bundles.

While it is unlikely that cortisone or corticotropin would materially change the fibrous process which is the principal defect in this disease, it is possible that they could affect the inflammatory reaction which has been described in the bronchi and alveolar septa and thus produce minor changes in symptoms. Because there is no evidence that these agents improve the diffusion of oxygen across the alveolar membrane which has been thickened by scleroderma, it is unlikely that they would significantly alter the course of scleroderma involving the lungs.

Cortisone and corticotropin should probably still be regarded as of unproved value in pulmonary scleroderma. If treatment is undertaken because of progressive or disabling symptoms, tests of pulmonary function will be helpful in deciding whether any physiologic change has occurred and whether treatment should be continued.

Other Collagen Diseases. In rheumatic fever, polyarteritis, and acute disseminated lupus erythematosus, pulmonary infiltrations and pleural effusions are sometimes observed. These may result from congestive failure, complicating bronchopneumonia, or the specific lesions of these diseases. Clinically it may often be difficult to determine the etiology. In 2 patients reported by Carey, Harvey and Howard[38] the severe pleuritic pain which was present in 2 cases of disseminated lupus erythematosus disappeared within 24 hours after the start of treatment with corticotropin. Soffer and Bader[39] also found that in 9 patients with disseminated lupus erythematosus the pleural effusions cleared within two weeks of the start of treatment with cortisone or corticotropin.

The details of treatment of these diseases are discussed in another chapter.

Nonspecific Pulmonary Granulomas

Cortisone and corticotropin have also been used to treat granulomas of less specific type or etiology than those which have been discussed in this chapter. A few cases have been reported[1,2,3] of granulomatous disease of the lung not attributable to exposure to toxic substances and with a histologic pattern that is not characteristic of Boeck's sarcoid or berylliosis. Clinically and physiologically these cases have a pattern similar to that described under Sarcoidosis Type II and Beryllium Granulomatosis, i.e., the pattern of alveolar-capillary block. Pathologically they have been found to have an extensive invasion of the alveolar capillary septa by a granulomatous process. These granulomas have been composed of epithelioid cells with large numbers of giant cells which have been of both the Langhans and foreign body type and have contained large amounts of doubly refractile lamellated crystalline material. Similar granulomas with the same type of crystalline material have been observed in lymph nodes.

West et al.[26] observed a young man who had the physiologic pattern of alveolar-capillary block and a granulomatous process in both lung and lymph nodes like that just described. During his first course of treatment with cortisone (100 mg. daily after larger doses on the first three days) they observed a decrease in dyspnea and on X-ray of the chest an incomplete but definite clearing of the reticular infiltration in the lungs and a decrease of hilar lymph node enlargement. A second biopsy of the lung showed replacement of the previously noted epithelial cells by hyalinlike material. Physiologic studies showed improvement in the arterial oxygen saturation after exercise, slight increase in oxygen diffusing capacity, and return to normal of the venous admixture in the arterial blood. Treatment was stopped after three weeks and subsequent unpublished observations have shown that a relapse to his pretreatment status occurred; re-treatment with cortisone produced no such significant change as occurred with the first course.

This same paper[26] contains a report of another case in which dramatic improvement on corticotropin and cortisone was observed. The patient was a young woman of 26 with increasing dyspnea, cyanosis, and cough for two years so severe in the preceding month that she had been confined to bed. On admission to the hospital she was profoundly anoxic and required an oxygen tent continuously. Three weeks after admission, having had no improvement, she was started on corticotropin. In Figure 38 the treatment and progressive improvement are charted. Physical signs and X-ray findings cleared simultaneously. In the two years since then she has required cortisone most of the time but in doses of only 50 mg. three times a week.

Austrian et al.[3] mention another patient in whom a biopsy of a peripheral lymph node showed a granulomatous lesion with birefractile crystals and numerous foreign body giant cells. In this patient severe alveolar-capillary block complicated by right ventricular failure was present. Treatment with cortisone produced no change in the clinical or physiologic status. Autopsy showed widespread pulmonary fibrosis with granulomatous lesions

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The details of treatment of these diseases are discussed in another chapter

(1) Chronic interstitial or restrictive fibrosis, of which uncomplicated silicosis is an example a condition producing inelasticity of lung tissue with restricted ventilatory capacity and exertional dyspnea One would not expect that this fixed fibrous tissue infiltration would be appreciably altered by cortisone

(2) Complicating obstructive emphysema with or without asthmatic symptoms Cortisone may bring relief in this condition by its antiallergic effects as in bronchial asthma or perhaps by reducing an acute inflammatory process in the bronchial and bronchiolar walls

(3) Complicating acute or chronic infection, bronchitis bronchiectasis, bronchopneumonia It has been shown that cortisone and corticotropin may act adversely on such conditions by reactivating an old infection or permitting the implantation of a fresh one

(4) Complicating tuberculosis Cortisone or corticotropin, especially if used for extended periods may result in reactivating an old tuberculous focus This is further discussed in the chapter on infection

With the wide use of cortisone and corticotropin certainly many patients with pulmonary fibrosis of one type or another have been treated with these hormones For the most part these cases are only noted in the literature in the rare instances associated with unfavorable side effects A few more direct observations have been made Ferris et al [29] described a patient with pulmonary fibrosis who was not improved by corticotropin and another who showed a moderate subjective improvement Kennedy et al [30] reported a patient with silicosis who received 100 to 160 units of corticotropin for 30 days with resultant improvement in cough sputum and dyspnea This improvement persisted one week after treatment was stopped Cortisone 200 mg daily was then given for a week again with relief of symptoms Chest X rays showed no change during the course of therapy It is not clear whether or not this patient had an associated emphysema

In unpublished studies based on experience in the authors clinic, the action of cortisone or corticotropin in long standing chronic pulmonary fibrosis without obstructive emphysema or asthma has been largely negative If however in an individual case symptoms are progressing and unrelieved a schedule of treatment similar to that recommended for granulomas may be tried

Physiologic tests of the pulmonary function of a patient will often determine whether sufficient obstructive emphysema is present for cortisone therapy to be effective If there is an element of emphysema this agent may bring real relief sometimes in doses as low as 25 mg daily

Other Pulmonary Conditions

Pulmonary Carcinoma The results to be obtained with cortisone and corticotropin in this disease may be considered in two categories (1) direct therapy and (2) replacement therapy following bilateral adrenalectomy

(1) Little benefit is to be anticipated in established carcinoma of the

in the hilar and mediastinal lymph nodes It could not be determined whether treatment with cortisone converted the pulmonary lesion from *granulomatous to fibrotic or* whether it was fibrotic when treatment was started

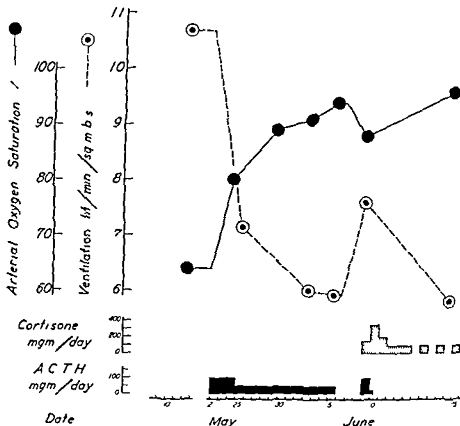


Fig 38 Chart showing the changes in resting ventilation and arterial oxygen saturation in association with cortisone and corticotropin therapy in a patient with pulmonary insufficiency of unknown etiology The measurements on May 12 were made while the patient was breathing air containing 25 per cent oxygen Subsequent measurements were made while the patient was breathing air containing 21 per cent oxygen (room air) (From West et al [25])

In these less well defined granulomatous diseases of the lung the inconstant and variable response to cortisone and corticotropin, as well as the conversion of the granulomatous lesion to a more hyaline and fibrous process is similar to the results which have been observed in Boeck's sarcoid and beryllosis The reasons for these variations in response are not clear but probably they are similar to those which have been discussed under Sarcoidosis

Silicosis, Chronic Fibrotic Pulmonary Disease

This large category of disabling pulmonary disease must be considered from the point of view of the action of cortisone and corticotropin in several aspects These may be listed as follows

sarcoidosis effect in a case with virtual blindness J A M A 147 824 1951

16 Lovelock F J and Stone D J *Cortisone therapy of Boeck s sarcoid* J A M A 147 930 1951

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19 Callston M Weinenfeld S Benjamin B and Rosenthal M B *Effect of ACTH in chronic lung disease a study of five patients* Am J Med 10 166 1951

20 Renold A E Forsham P H Maisterrena J and Thorn G W *Intravenously administered ACTH a preliminary report* New England J Med 244 796 1951

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28 Ferris B G Jr Affeldt J E Kriete H A and Whittenberger J L *Pulmonary function in patients with pulmonary disease treated with ACTH* A M A Arch Indust Hyg & Occup Med 3 603 1951

29 Krupp M A Saier M Keddie F Tanner R and Snell A M *Experience with cortisone and ACTH in a private clinic* California Med 75 6 1951

30 Kennedy B J Pare J A P Pump K K Beck J C Johnson L G Epstein N B Venning E H and Browne J S L *Effect of adrenocorticotropic hormone (ACTH) on beryllium granulomatosis and silicosis* Am J Med 10 134 1951

31 Van Ordstrand H S *Choice of drugs and dosage* A M A Arch Indust Hyg & Occup Med 3 583 1951

32 Weiss S Stead E A Jr Warren J V and Bailey O T *Scleroderma heart disease with consideration of certain other visceral manifestations of scleroderma* Arch Int Med 71 749 1943

33 Getzowa S *Cystic and compact pulmonary sclerosis in progressive scleroderma* Arch Path 40 99 1945

34 Spain D M and Thomas A G *The pulmonary manifestations of scleroderma an anatomic physiological correlation* Ann Int Med 32 152 1950

35 Bayles T B Stout C F Stillman J S and Lever W *The treatment of scleroderma with adrenocorticotrophic hormone preliminary observations* in Proceedings of the First Clinical ACTH Conference Philadelphia The Blakiston Company 1950 p 447

36 West J R McClement J H Carroll D Bliss H A Kuschner M Richards D W Jr and Cournand A *Effects of cortisone and ACTH in cases of chronic pulmonary disease with impairment of alveolar capillary diffusion* Am J Med 10 156 1951

37 Taubenhaus M and Lev M *Clinical and histological observations on a case of scleroderma treated with cortisone* A M A Arch Int Med 87 583 1951

38 Carey R A Harvey A McG and Howard J L *The effect of adrenocorticotropic hormone (ACTH) and cortisone on the course of disseminated lupus*

lung in the way of measurable effect upon the lesion In Pearson and Eliel's series[40] 2 cases of bronchogenic carcinoma were treated with cortisone or corticotropin without demonstrable change in the tumor A patient with tracheal carcinoma treated by Taylor Aver and Morris[41] had repeated biopsies before, during, and after therapy No changes were noted, and extension of the tumor occurred during treatment

(2) Of 18 patients with prostatic breast, or other types of carcinoma treated by Huggins and Bergenstal[4] by total adrenalectomy and subsequent maintenance on cortisone 2 with pulmonary metastases responded favorably One patient with primary bronchogenic carcinoma was not improved by adrenalectomy

Among other pulmonary conditions or diseases with pulmonary complications that respond favorably to cortisone or corticotropin therapy, trichinosis[43] and Loeffler's syndrome[44 45] may be mentioned

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10

Infections

Chester S Keefer

The general availability of crystalline cortisone has stimulated investigations of the relation between adrenocortical hormones and the course of many infections Also the question of the relation of adrenocortical hormones to resistance and the total defense forces of the body has been reopened

It has been demonstrated that in several diseases administration of cortisone or corticotropin to patients with a variety of infections is followed by a profound change in the clinical course There is often a decrease of fever disappearance of the symptoms and signs of intoxication and evidence of suppression of inflammatory processes These indications of improvement however, may be associated with an advance of the infection even though there are few or no overt symptoms or signs When administration of the hormones is stopped the severe symptoms of infection often reappear

This chapter will be devoted to a discussion of cortisone in infections It will conclude with a summary of some of the important points concerning the relation of adrenocortical hormones to resistance

Infections and Intoxications Treated with Adrenocortical Hormones

In Adrenalectomized Animals The relationship of adrenocortical hormones to resistance has been studied most extensively in adrenalectomized animals In 1941 the subject was reviewed by Perla and Marmorston[1] in their monograph entitled *Natural Resistance and Clinical Medicine* Later reviews by Hartman and Brownell[2] and Selye[3] are in essential agreement that adrenalectomy in animals decreases resistance to many infections and toxic agents Also there is increased susceptibility to anaphylactic shock and to histamine The theory that this decreased resistance is caused by a loss of cortical

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cortisone is given to these patients during an infection the dose should be adequate to maintain normal equilibrium but it should not be excessive in order that inflammation will not be suppressed The patient with Addison's disease is the clinical counterpart of the adrenalectomized animal with an infection

In Patients with Normal Adrenal Glands A variety of infections have been observed in man following the use of cortisone or corticotropin alone or in combination with antibacterial agents A number of warning signals have been posted in editorials and in special articles concerned with the problem of infection and resistance and the adrenocortical hormones because of evidence that cortisone can induce a reduction in resistance Inflammation is suppressed but the infection may spread in spite of symptomatic improvement This may occur without any evidence of the suppression of antibody formation or of direct stimulation of the growth of microorganisms In the light of these facts hormonal therapy should be administered with great caution in any patient with an infection

Adrenocortical Insufficiency in Acute Infectious Diseases

Before discussing the effects of cortisone or corticotropin in specific infections it is well to consider the question How often does adrenocortical insufficiency occur as a part of the clinical picture in acute infectious diseases?

During the course of infections in man Browne[14] has found an increase in the excretion of adrenocortical hormones in the urine This response of the adrenal gland to infection is probably nonspecific since a variety of injuries may cause a similar reaction The true significance of this increased excretion of hormones is not known So far Browne has not been able to demonstrate a quantitative reduction in the response of the adrenal gland to infection The possibility of partial failure of adrenal function during the course of some infections needs to be examined further

In the past some indirect evidence of adrenocortical insufficiency during the course of certain acute infections was developed from a study of the electrolyte pattern of the blood The changes noted are suggestive of adrenocortical insufficiency namely a decrease in sodium an increase in potassium and chloride hypoglycemia hemoconcentration and circulatory collapse [15] Furthermore there are scattered reports that the use of adrenocortical extracts and sodium chloride has been helpful in combating circulatory failure associated with infections Until more information becomes available such data must be interpreted as constituting only indirect evidence of adrenocortical insufficiency

When the adrenal glands are examined at postmortem they are found to have undergone profound histologic changes during the course of many severe infections In recent years Rich[16] has directed attention to the peculiar type of adrenal cortical damage associated with acute infections and its possible relation to circulatory collapse In his excellent essay he describes the damage to the adrenal cortex that follows various acute infections and gives clear illustrations There is necrosis of isolated cells and

function receives support from the observation that resistance can be raised by adrenocortical hormones

The mechanism by which adrenalectomy causes a decrease in resistance remains obscure That it decreases natural immunity to infection seems clear *Acquired immunity is not reduced however* and the capacity to produce antibodies remains substantially unchanged It has been suggested that the disturbances noted may be caused in part by alterations in electrolyte balance but this change cannot explain all of the observed facts

While animals with adrenocortical insufficiency can be made less susceptible to toxic agents following adrenocortical therapy, little or no benefit can be discovered in intact animals subjected to the same agents when cortical extracts are used Selye[3] has however been able to increase resistance to some extent in intact animals exposed to trauma cold and drug *The dosage of adrenocortical hormones may be a most important factor* since excessive amounts of these hormones given to intact animals exposed to infection may have a deleterious effect upon the resistance to the infection whereas small doses may have a slightly favorable effect

In Intact Animals When cortisone or corticotropin is given to intact animals subjected to infection there may be slight or no protection When large doses are given however, resistance to the infection is definitely suppressed This has been true in all animals including those receiving passive antibodies sufficient to increase resistance to the pathogenic agent This depression of resistance has been observed in a variety of bacterial viral and parasitic infections in animals including the hemolytic streptococcus,[4 5] the pneumococcus [6] the meningococcus [5] Brucella [8] Treponema pallidum [9] the staphylococcus [10] trichophyton [10] influenza virus [6] poliomyelitis virus [11] and malarial parasites [1]

This decreased resistance in intact animals following administration of cortisone or corticotropin is probably due to a nonspecific effect upon the processes of inflammation All those who have studied the tissue responses in these cases agree that inflammatory reactions are repressed and the infection is poorly localized Evidence that cortisone stimulates the growth of bacteria or decreases phagocytosis by leukocytes is lacking but there is evidence that it suppresses inflammation Kass[13] has suggested that the activity of the reticulo-endothelial cells may be inhibited by these hormones so that maximum activity of the clearing mechanism of the body is prevented

Here then is a paradoxical situation Animals with adrenocortical insufficiency have an increased susceptibility to infection and intact animals which have received large amounts of cortisone likewise exhibit an increased susceptibility The suppression of inflammation may account in part for the latter reaction, but the mechanism in these animals is unknown

In Patients with Adrenocortical Insufficiency It is well known that patients with Addison s disease are especially susceptible to infections and that conversely infection in these patients are likely to precipitate a crisis Introduction of the anti infective agents and of cortisone has been a great benefit to those with Addison s disease It is agreed however, that when

cases than in the controls during the second, third, and fourth weeks after treatment.

Typhoid Fever. It is well established that chloramphenicol is highly effective in the treatment of typhoid fever. After full doses of this antibiotic the fever and other signs of intoxication usually disappear within about 36 hours. When cortisone is given in conjunction with chloramphenicol to patients with typhoid fever, the temperature may return to normal within 15 to 50 hours depending upon the dosage.[illegible] When Smadel, Ley, and Diercks[79] gave 300 mg. of cortisone on the first day, 200 mg. on the second day, and 100 mg. on each of two successive days in addition to chloramphenicol, the average duration of fever was 15.5 hours. When cortisone is given alone to patients with typhoid fever, the clinical manifestations are completely controlled in some cases and partially controlled in others. As cortisone has no effect upon the bacteremia or upon typhoid bacillus, the exact mechanism by which its action takes place remains obscure.

It would appear, therefore, that chloramphenicol should be used in every case of typhoid fever and that cortisone can help greatly in shortening *many of the clinical manifestations of the disease. The cortisone dosage* producing the optimum effect appears to be that recommended by Smadel, Ley, and Diercks.[79] Chloramphenicol should be given in an initial dose of 3 Gm. followed by 1.5 Gm. every 12 hours for 9 days and then once a day for 10 to 14 days to prevent relapse or recurrence of symptoms.

Rocky Mountain Spotted Fever. A recent report by Woodward and his co-workers[illegible] suggests that when cortisone is used as an adjunct to chloramphenicol in the treatment of Rocky Mountain spotted fever the course of the disease is shortened and the symptoms and signs of intoxication are decreased. Cortisone was administered for only three days in doses of 200 mg. on the first day and 100 mg. on each of the two succeeding days. Chloramphenicol was given for at least 6 to 10 days. The authors were particularly impressed by the improvement observed when treatment was started late in the course of the disease. The results of combined therapy are sufficiently impressive in the few cases presented to stimulate others to study its effect.

Justification for the use of cortisone in Rocky Mountain spotted fever is found in the observation that degeneration of the fascicular cords of the adrenal cortex may occur in fatal cases and in the similarity of the clinical picture in severely ill patients to that noted in patients with adrenocortical insufficiency. These aspects of the disease, together with their relation to adrenocortical insufficiency and the use of replacement therapy, require intensive study both at the bedside and in the laboratory.

Pneumonia. Kass, Ingbar, and Finland[illegible] were the first to report the effects of corticotropin given alone without antimicrobial agents to 4 patients with pneumococcic pneumonia and to 2 patients with atypical virus pneumonia. The striking feature in all 6 cases was the rapid clinical improvement with relief of the symptoms and signs of acute toxemia. There was no effect upon the organism, and in 1 patient the bacteremia persisted for 36 hours. Another patient had an extension of the pulmonary process and developed

a transformation of the solid cords of the zona fasciculata into tubular structures containing an inflammatory exudate These changes have been observed at autopsy in patients who had had meningococcic, pneumococcic, and streptococcic infections, and diphtheria They have been noted especially in persons who died with an associated circulatory collapse

Prior to Rich's observations, and during World War I, Dietrich[1] made an extensive study of the anatomic changes in the adrenal glands during the course of various infections, including wound infections gas bacillus and streptococcic infections, and peritonitis In all of these the glands were damaged as shown by edema and a loss of lipoid material in the three layers of the cortex These changes were followed by necrosis complete destruction of cortical cells, and proliferation of the vascular connective tissue of the cortex These histologic changes are a part of the septic toxic process and differ from the metastatic septic processes in which there is a deposition of organisms in the capillaries, massive necrosis hemorrhage leukocytic infiltration, and abscess formation Many other observations have been made concerning the histologic changes in the adrenal cortex following infection, so that it is fair to say that a wide variety of infections have a deleterious effect upon the anatomic structure of the adrenal cortex

From such observations then, we may conclude that during acute infections especially those accompanied by signs of acute circulatory collapse the possibility of adrenocortical insufficiency should be considered and studies devised to determine whether this concept can be confirmed

Effect of Hormonal Therapy upon Specific Infections

Hemolytic Streptococcus Sore Throat Inasmuch as acute rheumatic fever follows tonsillitis caused by hemolytic streptococci it was only natural that cortisone should be studied in patients with the latter infection in an attempt to determine whether cortisone alone influences the course of the disease and whether acute rheumatic fever can be prevented by its use during the course of the acute infection Hahn and his co workers[18] studied a group of 174 patients with hemolytic streptococcus sore throat One half received no treatment and the other half received short courses of cortisone for five or six days in a total dosage of 500 mg

Cortisone had no effect upon the symptoms or physical signs of infection and the patients receiving the hormone had fever for a longer period than did the controls Suppurative complications developed in one of the cortisone treated patients and in 3 of the controls Rheumatic fever developed in 2 of the treated patients and in 5 of the controls The P R interval by electrocardiogram (ECG) was greater than 0 21 second in 5 of the treated patients and in 4 of the controls In short, cortisone had no effect upon the symptoms or signs of the acute disease, and in the doses employed, it did not increase the incidence of suppurative complications nor did it prevent the signs of acute rheumatic fever

There was no evidence that cortisone depressed the antistreptolysin response In fact, the titer of antistreptolysin was higher in the treated

closed by X ray examination of the lungs In patients with associated tuberculosis of the larynx the edema decreases and improvement follows In some patients the tuberculin reaction is reversed

These responses last only while the hormone is being administered Its withdrawal is often followed by a flare-up of all the symptoms and signs of the pulmonary lesions From these observations it is suggested that the effect of cortisone in active pulmonary tuberculosis is to suppress the inflammatory and the allergic hypersensitivity reactions and that when the cortisone is withdrawn the inflammatory reactions once again assert themselves

Active Tuberculosis Associated with Addison s Disease This is the one situation in which cortisone is indicated as replacement therapy in the presence of active tuberculosis The hormone should be given in the smallest daily dose that will maintain the patient in equilibrium

Inactive or Latent Tuberculosis A few cases have been reported in which patients with inactive or latent tuberculosis developed the active or disseminated form of the disease following hormonal treatment for rheumatoid arthritis or acute disseminated lupus erythematosus[34–37]

From all reports and studies so far it is plain that cortisone or corticotropin should be used in the treatment of tuberculosis only when there is associated Addison s disease Patients with active or latent tuberculosis should not receive hormonal therapy at the present time and all patients under prolonged treatment with hormones should be examined periodically for signs of active infection

Acute Peritonitis In patients dying from acute peritonitis and in animals with experimental peritonitis the lipid content of the adrenal cortex decreases significantly It has been postulated by some that this change may be followed by a failure in function and may account in part for the fatal termination To test this postulate Boling and his associates[38] treated a number of peritonitis patients with combined chemotherapy and hormonal therapy (cortisone or corticotropin) There was a rapid disappearance of toxicity and prompt return of normal gastrointestinal function These findings indicate that this combined therapy may produce better results than chemotherapy alone but further exploration and careful study are required

Waterhouse Friderichsen Syndrome ***Meningococcic Sepsis Purpura and Acute Circulatory Collapse*** This syndrome is often associated with massive hemorrhage into the adrenals or severe anatomic damage to the glands The prognosis is usually grave and recovery was very rare before the chemotherapeutic era At present treatment of the sepsis with anti infective agents of the shock with parenteral fluids and the use of cortisone as well as other adrenal hormones has resulted in recovery of a few patients[39 40] Certainly this is one infection in which replacement therapy with cortisone is indicated

Summary

The place of cortisone in the treatment of infections has not been definitely determined Certainly it should never be used as the sole agent in the treatment of infections

empyema One of the patients with primary atypical virus pneumonia had a severe and protracted course In short corticotropin can alter the course of both pneumococcic and atypical virus pneumonia insofar as symptoms of acute "toxicity" are *concerned but it has no effect upon the organism* In the experimental animal treated with cortisone and infected with pneumococcus it has been shown[8] that the inflammatory lesions in the lung are suppressed and that they contain an excessive amount of acellular fluid in which are many organisms

Trichinosis Cortisone and corticotropin effect symptomatic relief of trichinosis [3, 4] Fever edema and muscular pains decrease rapidly and improvement occurs promptly This is one of the first advances in the treatment of this parasitic infestation The symptomatic relief is related in some way to the antigen antibody reaction because in the experimentally produced disease in guinea pigs corticotropin does not prevent death when massive infection is present nor does it affect the number of parasites in the muscles The percentage of eosinophils in the circulating blood decreases temporarily

Keratodermia Blennorrhagica Associated with Gonococcic Arthritis Cortisone has been shown to have a beneficial effect upon the skin lesions of keratodermia blennorrhagica [5] associated with gonococcic arthritis It therefore deserves further trial in this dermatologic condition

Malaria When given to monkeys with malaria [1] cortisone causes an increase in the parasitemia in the postcritical phase and the response resembles that which follows malaria Lymphemia and a decrease in the size of the lymph nodes and spleen also occur Treatment of the chronic or latent *stages of the infection provokes a recrudescence which may be very severe* These studies suggest that cortisone and corticotropin are contraindicated in the treatment of malaria The same observation has been made in man [6]

Leprosy Lepromatous lesions have been observed to decrease under treatment with corticotropin [7] and it is suggested that this is the result of a change in the local tissue reactions

Tuberculosis ***Experimental Infections in Animals*** It is generally admitted that both cortisone and corticotropin suppress the inflammatory lesions of tuberculosis in the mouse guinea pig and rabbit The mortality increases in hormone treated animals and the lesions become more necrotic and contain larger numbers of bacilli [8–31] There is some evidence that the beneficial effect of streptomycin may be partly lost by the addition of cortisone in the management of experimental infections [3] All the studies in experimental tuberculosis suggest therefore that cortisone enhances the severity of tuberculous infection and that it acts by altering the tissue *reaction* around the bacilli rather than by any direct effect upon the organisms themselves

Active Tuberculosis in Human Beings When cortisone or corticotropin is given to patients with active pulmonary tuberculosis a striking change occurs during the period of therapy [33] There is defervescence, improvement of appetite and a temporary regression of signs of inflammation as dis

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The combined use of antimicrobic agents and cortisone needs further study especially in patients with adrenal insufficiency or with acute circulatory failure associated with infections in which there are signs of adrenocortical insufficiency

In experimental animals cortisone enhances tuberculosis and infections due to meningococci hemolytic streptococci, staphylococci pneumococci, influenza virus poliomyelitis virus, Brucella, trichophyton, treponema, and malarial parasites

Cortisone produces clinical improvement in patients with Addison's disease associated with tuberculosis when given in small doses (50 mg a day) in combination with streptomycin

Cortisone may produce clinical improvement with relief of symptoms and signs of acute intoxication in patients with typhoid fever Rocky Mountain spotted fever pneumococcic lobar pneumonia, and atypical virus pneumonia The infective agents are not affected, and relapses and complications are not prevented When cortisone is used in the management of such patients it should always be combined with the most effective antimicrobic agent The precise indications for cortisone treatment in such infections are unknown

While cortisone is being used for the treatment of any chronic disease, such as rheumatoid arthritis or disseminated lupus erythematosus the patients should be followed most carefully for signs of infection It is established that when patients undergoing treatment with cortisone develop an intercurrent infection many of the common signs of infection such as fever and the associated symptoms of intoxication may be absent When latent tuberculosis becomes active in a patient under cortisone treatment the symptoms may be minimal in spite of the activity and progression of the disease It is well therefore, to study all patients under cortisone treatment carefully for signs of infection

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11

Eye Diseases

Alan C. Woods

In 1949, shortly after Hench and his associates in the Mayo Clinic published their paper on the dramatic effects of cortisone and corticotropin upon the subjective symptomatology of rheumatoid arthritis, it was noted by several observers that these agents had a similar effect upon the acute nongranulomatous iritis so often associated with rheumatoid arthritis. Although these substances were then in scant supply and only a few cases of ocular disease could be treated, it soon became evident that they had a remarkable effect upon various other ocular inflammations. There was no information then available on the therapeutic range or limitations of these hormones, the proper dosage or methods of administration for ocular disease, or the mechanism through which they exerted their effect. A good deal was known, however, of their general physiologic action, and certain definite contraindications to their use (though by no means all) were recognized.

Ophthalmologists were therefore confronted with a fourfold problem, which may be summarized as follows: (1) to determine the therapeutic range and limitations of these agents in ophthalmology, i.e., to ascertain the extent of a favorable clinical therapeutic action and the ocular conditions in which they were effective; (2) to determine the proper dosages and the optimum methods of administration in ophthalmic disease; (3) to determine the effect of these hormones upon various experimental ocular lesions and to explore the mechanism of their action in this field; (4) in the light of clinical and experimental investigations, to determine the ocular conditions in which hormonal therapy might have a deleterious effect and be specifically contraindicated.

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The portions of this report emanating from the Wilmer Ophthalmological Institute were supported by a grant from the National Institutes of Health, U. S. Public Health Service. This chapter is an extension and amplification of a paper by the same author in the British Journal of Ophthalmology 36: 401, 1952.

As these substances came into more abundant supply, ophthalmologists addressed themselves to these problems with enthusiasm In the short period of five years, a mass of information has been collected on the use of cortisone and corticotropin in ophthalmology Hydrocortisone became available later than cortisone and consequently has received less intensive investigation The indications are, however, that its action is similar to that of cortisone, and possibly even more effective The evidence now available makes a formidable and remarkably uniform total The purpose of this report is, therefore, to assemble the information already obtained and to point out what has been established and what requires further investigation

Range and Limitations of Adrenocortical Therapy in Eye Diseases

In the Gifford Memorial Lecture[1] delivered in 1951, the paucity of the reports then existing was pointed out The material on which this lecture was based was a series of cases of ophthalmic disease treated with cortisone and corticotropin in New York Hospital and made available through the courtesy of Dr John McLean,[2] and a similar series treated in the Wilmer Ophthalmological Institute Study of these cases 397 in all, permitted certain broad conclusions Since this lecture, numerous other reports confirming the original findings have appeared in the literature [3-4] These conclusions were

In certain inflammatory conditions of the eye, especially those affecting the cornea uveal tract, and external eye the parenteral administration of cortisone or corticotropin or the topical administration of cortisone is followed in a high percentage of cases by dramatic control of the inflammatory *and exudative phases of the disease These agents do not affect the cause of* the disease but, rather, influence the reaction of tissues to the cause or irritant

In many diseases which are favorably influenced there is a definite tendency for the inflammation to recur after cessation of treatment

In certain edematous and inflammatory conditions—especially secondary glaucoma inflammations of the retina and optic nerve, edematous corneal grafts and probably in syphilitic interstitial keratitis—the action of cortisone and corticotropin is variable and cannot be accurately predicted

In some hemorrhagic and exudative conditions such as Coats's disease Eales's disease, malignant exophthalmos, diabetic retinopathy, and retrolental fibroplasia no consistent therapeutic results have as yet been demonstrated

In degenerative disease whether of the cornea retina, or uveal tract these agents are totally without effect

The material available from other investigators and from our further experience in the Wilmer Ophthalmological Institute (where the number of cases treated is now more than double that of those reported[1]) permits elucidation and definition of broad general principles for the use of these agents in ophthalmic disease *The favorable action and the limitations of cortisone*

and corticotropin as indicated by the information available at present may be summarized as follows

External Diseases

Inflammations of the external eye are the result of either allergic toxic or physical trauma or of a degenerative process or are evidence of an exogenous or endogenous infection The therapeutic range of cortisone and corticotropin in external ocular inflammations varies greatly according to the cause of the disease

In acute nonbacterial inflammations of the external eye, the action of these hormones is usually spectacular Here the inflammation secondary to the physical allergic, or toxic trauma is in itself the harmful reaction which, if severe long-enduring or repeated, ultimately produces actual damage to the cells and organic change in the eye Hormonal therapy, either parenteral or topical usually controls the inflammation secondary to physical or toxic trauma interposes a shield between the cells and the irritant and facilitates prompt recovery without residual damage

Allergic reactions in the eye are usually acute insults and are self limited They may however appear to be chronic when they are the result of a hypersensitivity to bacterial antigens and intoxication arises from a chronic focus of infection In acute reactions such as allergic conjunctivitis vernal catarrh phlyctenular keratoconjunctivitis and episcleritis, if cortisone or corticotropin therapy is continued throughout the natural life of the reaction the control of inflammation and exudation may simulate a complete cure Within 24 to 48 hours after institution of treatment the eyes become white and free of inflammation when cortisone or corticotropin is discontinued after 6 to 10 days of treatment if the reaction has burned out the eyes remain free of symptoms until the allergic insult is repeated In the chronic reaction in which the body is apparently unable to free itself of the intoxicating allergen a similar suppression of inflammation is experienced but unless steps are taken to remove the intoxicating allergen or to desensitize the patient there will be an almost immediate return of inflammation when treatment is terminated It is in the allergic reactions however that cortisone and corticotropin reach their greatest usefulness In more than 90 per cent of external allergic inflammations the use of these agents gives almost complete symptomatic relief and if properly continued complete control of the acute attacks The availability of hormonal therapy with resultant symptomatic improvement does not relieve the ophthalmologist of the duty of determining if possible the cause of the allergic intoxication and taking proper steps to remove the same Otherwise acute attacks will recur upon renewal of the stimulus in the chronic reaction the recurrence will often be immediate on cessation of treatment

One form of external allergic reaction contact dermatitis requires special mention Dermatologists are almost unanimous in reporting that the parenteral use of cortisone or corticotropin or the topical use of cortisone has no effect whatsoever upon contact dermatitis or drug allergy On the

other hand Carey and his associates[13] have reported that intensive cortisone or corticotropin treatment of patients with skin eruptions secondary to drug allergy results usually in prompt and complete control of the dermatitis but there is a marked tendency for it to recur after termination of treatment The question is of especial interest to ophthalmologists since they so frequently encounter a hypersensitivity to atropine and other alkaloids used routinely in the eye Our experience has been that vigorous parenteral treatment with cortisone or corticotropin is followed by prompt subsidence of the lid dermatitis and that atropine or other alkaloid can be used without reaction as long as the hormonal treatment is continued A similar but less intense effect may be obtained by applying cortisone topically to the conjunctival sac Though it is difficult to attribute the subsidence of the dermatitis to this therapy the fact that the patient can be challenged with the alkaloid without reaction while under hormonal treatment indicates a cause and effect relationship

It has been stated that cortisone is without effect in degenerative disease Although it has no therapeutic action on the underlying condition nevertheless topical cortisone is of value in controlling the inflammation secondary to a degenerative keratitis Thus in a band keratitis with calcium carbonate and phosphate crystals beneath the epithelium and occasional erosion through the epithelium the photophobia and conjunctivitis can often be successfully controlled by instillation of cortisone or hydrocortisone ointment in the conjunctival sac Unless an active underlying granulomatous uveitis is present there is no contraindication to the prolonged use of topical cortisone and it frequently gives more symptomatic relief than any other treatment

In exogenous or endogenous infections the action of cortisone and corticotropin is limited at best to control of the inflammatory reaction These hormones have no antibiotic action and do not affect the invading organisms Further their ability to control inflammation is in direct proportion to the severity of the stimulus If the infecting organisms are of high toxicity and especially if they produce tissue destruction or necrosis the inflammatory reaction may be well beyond the therapeutic range of either cortisone or corticotropin Therefore any therapeutic action they have in bacterial infections is limited in scope and related to the severity of the inflammatory stimulus In minor infections they may give symptomatic relief but if the natural factors of resistance or some form of therapy does not actually destroy the infecting organism the bacteria continue to grow and the use of cortisone or corticotropin only masks the symptoms *Thus though cortisone and corticotropin are useful agents in bacterial conjunctivitis or in infected corneal ulcers insofar as they reduce inflammation and pain their use carries with it the risk of masking symptoms and lulling both the patient and ophthalmologist into a false sense of security*

In the treatment of deep seated endogenous infections of the cornea an additional question arises In many instances the inflammatory, neovascularization and fibroblastic processes which accompany a keratitis are defense

and repair phenomena Obviously such phenomena should not be suppressed unless other adequate specific therapy is available This principle is well exemplified by a case of abscess of the cornea On admission there was conjunctival inflammation, marked chemosis and beginning vascularization of the cornea The patient was placed immediately on hormonal therapy which produced partial clearing of the external inflammatory reaction and a subsidence of the chemosis The abscess itself was unchanged if anything it progressed After one week of hormonal treatment the causative organism had been isolated and its sensitivity to antibiotics and sulfonamides determined Specific therapy was then begun and the abscess promptly healed

Since cortisone and hydrocortisone have no antibiotic effect but may control the inflammation of infection and give symptomatic relief at the risk of masking symptoms local use of a combination of cortisone and an antibiotic may be considered Such combined treatment has been used for some time in the Wilmer Institute and no antagonistic action between cortisone or hydrocortisone and any antibiotics or sulfonamides has been noted Recently the possibility of such an antagonistic or inhibitory action between cortisone and various antibiotics *in vitro* and *in vivo* was investigated by Lepri [14] and no antagonistic effect was found Combinations of cortisone and neomycin and of cortisone and bacitracin in ointment are already on the market In infections in which the invading organism is neomycin or bacitracin sensitive these combinations have already proved their worth, giving early symptomatic relief together with the necessary antibiotic action However one or two antibiotics even though they may have a wide spectrum are insufficient Combinations of cortisone or hydrocortisone with various other antibiotics should be made available to facilitate the use of hormonal therapy with the specific antibiotic to which the organism is most sensitive

The underlying principle for the use of cortisone and corticotropin in external ocular disease is that in acute inflammation from allergic or physical trauma these hormones will shield and protect the tissues from the resultant toxin or irritant and so prevent the inflammatory reaction Since allergic or physical trauma is usually self limited treatment throughout the natural life of the tissue reaction may simulate a complete cure If the inflammation is the result of actual bacterial infection the use of these agents should always be accompanied by proper chemotherapy or antibiotic therapy to destroy the infecting organisms In chronic or deep seated external ocular infections not only should the use of cortisone or corticotropin be accompanied by appropriate therapy directed at the cause of the disease but the question whether the inflammation is a defense and repair reaction should also be considered before hormonal therapy is instituted

Uveal Disease

In evaluating adrenocortical therapy in uveitis the fundamental differences between nongranulomatous and granulomatous uveitis and between acute and chronic uveal inflammation must be kept clearly in mind

Nongranulomatous uveitis is believed to be either a hypersensitivity phenomenon or the result of acute physical or toxic trauma The usual causes are either a bacterial hypersensitivity resulting from a former infection, or a reaction to operative or other trauma It is characterized clinically by acute inflammation, edema, and sometimes a fibrinous exudate, without primary organic changes in the tissues The insult is usually acute and the tissue reaction limited A severe attack may produce organic damage, but as a rule the early attacks clear without residua, and organic damage occurs only upon repeated attacks In the chronic allergic reaction in which the body is unable to free itself from the intoxicating allergen, the tissue reaction may be prolonged until the hypersensitive state is exhausted Histologically the reaction is characterized by edema serous exudation, and diffuse lymphocytic infiltration [16] Classic examples of nongranulomatous anterior uveitis are the acute iritis so often associated with rheumatoid arthritis or an old gonococcal infection and the noninfectious postoperative cyclitis A similar example in the posterior uvea would be the intense subretinal edema and vitreous exudation seen as part of the focal ocular tuberculin reaction

Granulomatous uveitis is believed to be caused by the actual invasion of the uveal tract by living organisms which cause granulomatous disease It is essentially a chronic infection The recognized granulomatous ocular diseases are tuberculosis syphilis brucellosis, and viral yeast, and fungus infections There are probably many unrecognized causes A classic granulomatous uveitis is characterized by low-grade chronic inflammation and nodular infiltration of the tissues, with gradually developing organic changes, tissue destruction and a replacement by fibrous tissue Histologically the cellular infiltration consists of epithelioid cells, lymphocytes, macrophagic cells large mononuclears, and fibroblasts Classic examples would be a chronic tuberculous uveitis in an individual with low sensitivity to tuberculin or the chronic diffuse choroiditis of early syphilis

In the classic forms of nongranulomatous and granulomatous uveitis the two types of inflammation (the acute intense inflammation caused by the hypersensitivity reaction and the chronic, comparatively low grade inflammation caused by infection) can be readily differentiated However nongranulomatous uveitis of the chronic type or that which occurs after repeated acute attacks and resultant tissue damage may closely simulate the picture of granulomatous uveitis Similarly granulomatous uveitis may show a confused picture Organisms which cause typical granulomatous changes in the tissue may at the same time produce a bacterial type of hypersensitivity Once such a hypersensitivity is established, a secondary allergic reaction may be evoked by the various fractions of the bacterial antigen It is clearly recognized that this occurs in tuberculosis and probably in other granulomatous diseases Thus in the same eye there occurs the picture of a nongranulomatous reaction superimposed upon a granulomatous focus In highly sensitized tissue the allergic reaction may be so intense that it masks the true underlying granulomatous nature of the disease In other cases the dual

nature of the reaction may be quite evident—violent external inflammation associated with typical granulomatous changes in the anterior uvea, or the very common picture of a massive choroidal exudate surrounded by a zone of subretinal edema

The importance of this concept of two types of inflammation occurring in the same eye is of paramount importance in evaluating hormonal therapy in granulomatous uveitis Cortisone and corticotropin tend to suppress the inflammation and exudation due to allergy irritants physical trauma or bacterial infection although the extent of this inhibitory action varies with the character and intensity of the stimulus causing the inflammation *Therefore in evaluating the therapeutic effect of hormonal therapy one must consider the type of inflammation suppressed and the value of such suppression* Since different concepts of the etiology of uveitis are in vogue in different clinics and varying terminology and diagnostic criteria are often employed it is somewhat difficult to assess the results reported in the literature However, when due allowances are made for such factors analysis of these reports gives remarkably uniform and consistent data

Nongranulomatous Uveitis In classic acute inflammations of the anterior uvea, whether caused by allergic insult or postoperative reaction without infection cortisone and corticotropin exert their most dramatic and consistent effects In approximately 80 per cent of patients with acute iritis a prompt favorable reaction is noted within 48 hours varying from improvement to complete subsidence of ciliary congestion and edema of the iris as well as disappearance of cells and fibrin from the anterior chamber If treatment is continued thereafter throughout the natural course of the disease this improvement may simulate a complete cure In the postoperative type without infection both cortisone and corticotropin have a pronounced effect in controlling pain and inflammation

In the so-called chronic form of nongranulomatous iritis or iridocyclitis the reported results are not so spectacular A favorable reaction varying from improvement to complete subsidence of inflammation is observed in approximately 60 per cent of the cases However unless the offending allergen or underlying stimulus is eradicated, there is a tendency for the inflammation to return after cessation of treatment

Nongranulomatous disease of the posterior uvea is variously termed nongranulomatous choroiditis acute choroiditis acute diffuse choroiditis In its typical acute form it is characterized by intense generalized edema of the choroid and clouding of the vitreous usually without heavy organized opacities The more chronic form is characterized by ill defined exudates with surrounding subretinal edema These ill defined exudates may be nongranulomatous foci where the cellular infiltration is most intense occasionally they may be true granulomatous lesions with surrounding edema that is the result of an allergic tissue reaction due to a bacterial hypersensitivity produced by the invading organisms responsible for the basic granulomatous disease—a nongranulomatous process superimposed upon a granulomatous one

In the acute edematous form without exudation or when ill defined exudates are merely foci of increased cellular infiltration, the use of cortisone or corticotropin is usually followed by complete regression of all objective symptomatology If adequate treatment is maintained thereafter over the natural course of the reaction this may simulate a complete cure However, if the ill defined exudates are actual granulomatous foci with a secondary allergic reaction around them the action of cortisone and corticotropin may be limited to control of the subretinal edema circumscription of the exudate, and *clearing of the vitreous In such cases unless other therapeutic* procedures have controlled the basic disease process recurrences are frequent when hormonal therapy is discontinued The various reports indicate that this type of favorable reaction may be expected in approximately 80 per cent of patients treated Almost all observers agree that to obtain a favorable result in posterior uveal disease treatment should be more prolonged and intensive than that required in the anterior form

Differences of opinion appear in the various reports on the incidence of recurrences of acute uveal inflammation after hormonal therapy This probably is the result of variation in the periods of observation after treatment A study at Wilmer Institute where the period of observation in the early cases is now almost five years indicates that in recurrent types of uveal disease such as acute nongranulomatous iritis associated with rheumatoid arthritis *if specific therapy directed at the cause is not instituted or is not* successful recurrences after primary control of the inflammation by cortisone or corticotropin therapy occur with the same regularity as before treatment

Granulomatous Uveitis Granulomatous inflammation of the anterior uvea (chronic uveitis) is usually characterized by chronic low grade inflammation and organic changes in the iris and ciliary body, with secondary corneal and lens changes It may smolder for months or years and may undergo exacerbations with periods of acute inflammation which probably are local hypersensitivity reactions If hormonal therapy is used during an acute exacerbation an immediate result favorable in the sense of control of inflammation and pain will usually ensue If used in the chronic phase when the predominant cause of the low grade inflammation is infection the response to such therapy is less striking and recurrences are prompt and frequent after treatment is terminated Organic changes and nodules in the iris are not usually affected by hormonal therapy If they appear to regres the improvement is almost certainly the result of a spontaneous subsidence of the inflammatory reaction rather than a specific action of the hormones on the cause of the granulomatous disease The experience of various investigators indicates that some control of inflammation occurs in approximately 60 per cent of cases of chronic granulomatous uveitis but that relapses are frequent

Granulomatous disease of the posterior uvea is variously called granulomatous choroiditis chronic choroiditis focal choroiditis chronic exudative choroiditis circumscribed plastic choroiditis deep foglike choroiditis and

various other names It is essentially an exudative disease with tissue destruction It is not readily influenced by cortisone or corticotropin therapy, an apparently favorable result being reported in only about one third of the cases and in these cases the favorable action is usually limited to circumscription of the exudates control of any surrounding subretinal edema and some clearing of the vitreous—in short control of a secondary nongranulomatous allergic reaction If the exudates gradually absorb without gliosis such absorption should not be considered a cure It may be caused by suppression of the inflammatory reaction of infection the natural forces of resistance or adjuvant therapy and should not be interpreted as resulting from a specific action of the hormones on the cause of the disease

Recurrences of granulomatous choroiditis after cessation of hormonal therapy are frequent How frequent cannot be said for the different terminology used in various reports and the absence of exact data on treatment make an accurate analysis impossible If one can judge from a consulting practice where in general only the worst cases are seen severe recurrences after hormonal therapy appear to be the rule

The basic principle in the use of hormonal therapy in granulomatous uveitis appears to be that such therapy may be a two-edged sword Cortisone and corticotropin tend to suppress inflammation and exudation whether produced by a hypersensitivity reaction or by infection Since the inflammatory reaction due to allergy is violent and may be destructive its suppression is a desirable aim On the other hand the inflammation due to chronic infection is low grade and as pointed out, may be considered a reparative phenomenon In granulomatous uveitis therefore the question is how to use hormonal therapy to control a destructive allergic inflammation and yet not interfere with the reparative processes which accompany the inflammation of infection There is no clear answer Until the situation is clarified by further study the wisest rule is that cortisone or corticotropin should not be used in granulomatous uveitis unless clinical evidence of a serious secondary allergic inflammation is present Their use in such cases should always be guarded—never prolonged—and if possible hormonal therapy should always be accompanied by specific chemotherapy or antibiotic therapy

Two types of granulomatous uveitis that require special mention are sarcoidosis and sympathetic ophthalmia

Sarcoidosis Early attempts to control ocular complications of sarcoidosis by the parenteral use of cortisone or corticotropin or the topical use of cortisone were as a rule disappointing although favorable results occasionally were reported Comparatively recently it has been shown that under intensive intravenous corticotropin therapy the mediastinal cutaneous and ocular lesions of sarcoidosis melt away only to recur promptly when treatment is terminated The eye however offers a unique opportunity for administering sustained therapy which may possibly control the local disease In the Wilmer Institute several proven cases of ocular sarcoidosis were treated intensively with intravenous corticotropin and dra

matic resolution of the lesions ensued There were prompt recurrences after cessation of treatment The disease was again brought under control by intravenous corticotropin therapy and thereafter the patients were given sustained treatment with topical cortisone ointment in the conjunctival sac Over a period of observation, now up to eight months in 1 case, there have been no recurrences What the end result will be is unpredictable but in view of the gravity of the disease and the absence of any other form of therapy this treatment appears justified

Sympathetic Ophthalmia Haik, Waugh, and Lyda[16] have recently assembled and analyzed the results of cortisone and corticotropin therapy in 72 cases of sympathetic ophthalmia Regardless of the severity or duration of the disease an immediately favorable result was obtained in 47 or 64 per cent of the cases After termination of therapy 18 of these cases relapsed but the disease was again brought under control with further treatment In early cases the favorable results were even more striking approximately 80 per cent being controlled by cortisone or corticotropin therapy This is a significantly higher percentage of favorable results than that obtained with any other form of treatment Moreover, it appears quite possible that the failure rate might have been lowered still further if intensive intravenous corticotropin therapy had been used in the unfavorable cases Sympathetic ophthalmia is a prolonged but ultimately self limited, disease It therefore appears that prolonged treatment throughout the natural course of the disease may be necessary Because of the gravity of this condition patients who do not respond to the usual hormonal therapy given parenterally may be treated with corticotropin intravenously with proper precautions later cortisone may be administered topically

Inflammations of the Nerve and Retina

It is almost impossible to evaluate the reports of favorable action of cortisone and corticotropin in optic neuritis A number of authors have observed remarkable improvement in optic and retrobulbar neuritis after the use of these agents others have reported entirely negative results All those citing favorable results have recognized that many forms of optic neuritis whether produced by demyelinizing disease syphilis or undetermined causes have a natural tendency to sudden and spontaneous remission Therefore, in any individual case it is difficult—often impossible—to state whether the observed improvement is *post hoc* or *propter hoc* The general impression appears to be that favorable resolution of the optic neuritis is noted in more than one half of the cases treated with cortisone or corticotropin and that this result is related to the therapy Until the exact etiology of optic neuritis is better understood and the mechanism of the action of these hormones is established, it will probably be impossible to relate the observed improvement definitely to the hormonal therapy On the basis of the information available the use of these agents is indicated in optic and retrobulbar neuritis, certainly as a trial procedure

In central serous retinopathy, if treatment is instituted before degenerative changes in the retina have occurred the results of cortisone or corticotropin therapy appear remarkably good subjective and objective improvement usually beginning after 2 to 3 days treatment, with subsidence of the central serous exudation occurring in 7 to 10 days Recurrences after cessation of treatment are not uncommon

In acute exudative retinitis (Coats s disease) which may be either an acute exudative disease in the external retina or a subretinal hemorrhagic reaction there is some equivocal evidence that in the early stages before detachment and gliosis have occurred cortisone or corticotropin may check the remorseless course of the disease A consistently favorable reaction however has not yet been demonstrated Only a few such cases have been treated and failures appear to be more frequent than successes Further investigation of the action of cortisone and corticotropin in the exudative type of Coats s disease is justified

In other forms of retinopathy such as the various hemorrhagic types, i e diabetic retinopathy athero- and arteriolosclerotic retinopathies Eales s disease leukemic retinitis the use of cortisone and corticotropin has given uniformly disappointing results A large number of diabetic retinopathies have been treated with topical cortisone and no real improvement has been noted It has been demonstrated that parenteral treatment with cortisone or corticotropin is possible in diabetics if the insulin dosage is properly increased In a few cases of diabetic retinopathy treated under this regimen, the results have been disappointing and any visual improvement probably is the result of spontaneous absorption of vitreous hemorrhage rather than any alteration in the retinopathy Recently reported experimental evidence discussed in a subsequent section of this chapter indicates that therapy with cortisone or corticotropin may actually be contraindicated in diabetic retinopathies

Miscellaneous Eye Diseases

In several ocular diseases there has been or is still considerable difference of opinion concerning the therapeutic action of cortisone and corticotropin Chief of such conditions are the exophthalmos of Graves s disease cloudy corneal grafts, secondary glaucoma and retrolental fibroplasia

The Exophthalmos of Graves' Disease In only a few cases in this category has treatment with these hormones been reported Fitzgerald and his co-workers[7] cited 2 cases in which a conspicuously favorable result was obtained Others[1 2 5] have observed no effect whatsoever Experimentally Smelser and Ozanics[17] have shown that cortisone and corticotropin have no effect upon the experimental exophthalmos of guinea pigs The rationale of hormonal therapy in thyrotropic exophthalmos appears to be the fact that a marked increase occurs in the water volume of the orbit and the assumption that the use of these agents decreases capillary permeability Since the results of treatment reported thus far are contradictory further exploration is indicated

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they reported 14 premature infants with retrolental fibroplasia treated with large doses of corticotropin In all of these progression of the disease was inhibited In 3 of 5 untreated controls the disease progressed In a more recent paper they and their associates divide the acute phase of the disease into five stages and point out that if the treatment is to be successful it must be instituted in the first or second stage In 30 cases in these categories treated with corticotropin success was obtained in 16 and failure or indeterminate results in 14 In 36 similar untreated control cases spontaneous regression occurred in 25 and progression of the disease in only 11 Combining their series they found no statistical difference in the progress of the disease between the treated and the untreated cases and concluded that corticotropin has no effect upon the course of the disease This observation is in accord with that of the majority of investigators although Scheie et al [5] who studied the effects of both cortisone and corticotropin have reported isolated successes *Since corticotropin therapy in premature infants is* attended by a high mortality and morbidity and all the weight of evidence is against such treatment s having any therapeutic value no further exploration of its use in retrolental fibroplasia appears justified

Degenerative Disease

The statement that in degenerative disease whether of the cornea retina or uveal tract these agents are totally without effect[1] requires explanation and amplification

Retinal Degeneration Degenerative disease of the eye may in some instances be secondary to inflammation or exudation and the resultant loss of vision may stem from both the inflammatory and the degenerative factors Control of the *edematous or inflammatory* phase *may therefore give subjective* visual improvement and at the same time check the progression of the secondary degeneration For example in central serous retinopathy there may be a beginning macular degeneration secondary to the localized subretinal edema Control of the serous retinopathy may therefore result in restoration of the retina to proper position and thus improve vision and check the progress of the macular degeneration The retinal degeneration which has already taken place remains unaffected Essential degenerations such as corneal dystrophies juvenile or senile macular degenerations hyaline *degeneration familial retinal degeneration* and degeneration secondary to hemorrhage are totally unaffected by the adrenocortical hormones Two conditions—pigmentary degeneration of the retina and fibrinoid degeneration of the connective tissue—merit special mention

Pigmentary Degeneration A number of cases of pigmentary degeneration of the retina have been treated by parenteral injections of cortisone or corticotropin and by the topical use of cortisone Careful efforts have been made to detect any improvement by following the visual acuity the light sense and the visual fields Some moderately encouraging results have been *recorded in a few* cases by McLean Gordon and Koteen and in one case by

Keratoplasty A number of cases of keratoplasty associated with early clouding and vascularization of the graft have been treated with cortisone topically or parenterally, or with corticotropin parenterally Treatment with these agents was usually instituted from the second to fifth week after operation and after clouding or vascularization of the graft had appeared If treatment is instituted within the first three days after clouding is observed, 50 per cent or more of the cases show a clearing of the graft and inhibition of vascularization therefore what threatened to be an unfavorable result has been transformed into a favorable one Topical cortisone appears to be the preferable method of treatment Treatment must be instituted before the changes are established and irreversible Maumenee[18] has recently reported experiments indicating that delayed clouding of the graft may be related to an allergic reaction to the donor graft by the recipient Experimental studies discussed in a later section of this chapter, indicate that cortisone inhibits neovascularization of the cornea In view of this experimental work and the favorable clinical results reported, the topical use of cortisone in early clouding and vascularization of corneal grafts appears indicated Though treatment should be instituted early it should probably be delayed until two weeks after operation in order not to interfere with firm union of the graft

Secondary Glaucoma The action of cortisone and corticotropin in secondary glaucoma apparently is quite unpredictable Blake Tasanella, and Wong[19] have reported 4 cases of secondary glaucoma in which the tension was controlled by the use of corticotropin Other observers have also noted that in some patients hormonal therapy is followed by a control of tension in secondary glaucoma but in other cases these hormones have not had any effect upon this condition Tillett[20] has recently reported a study which indicated that in patients with normal eyes the ocular tension is unaffected by parenteral use of corticotropin The explanation of these conflicting results may be that when the secondary glaucoma is the result of acute inflammation or exudation the control of such inflammation may restore a normal balance, but if the secondary glaucoma is due to organic changes or blocking of the angle by inflammatory debris these hormones will have no effect From the clinical viewpoint there appears to be little reason to use either cortisone or corticotropin in secondary glaucoma unless active ocular inflammation is present

Retrolental Fibroplasia Reese and Blodi[21] have argued that retrolental fibroplasia is essentially an angioplastic or angiomatous process although in some cases the early dilatation of the retinal vessels may be absent that many of the infants showed skin angiomas, that the adrenal pituitary axis is not well developed in early infancy that corticotropin appears in the placenta only in the last three months of pregnancy that premature birth deprive the infant of corticotropin, and that premature infants show a deficiency of 17 ketosteroids in the urine—all indicating a relative corticotropin deficiency It was therefore logical to postulate that retrolental fibroplasia might be related to such a deficiency In their first communication

any action in scleromalacia perforans Mooren s ulcer, or marginal dys trophies Further exploration of these possibilities is indicated

Administration and Dosage of the Adrenocortical Hormones in Eye Diseases

The methods of parenteral administration of the adrenocortical hormones and corticotropin are well known In general the same methods are used in ophthalmic disease When cortisone and corticotropin were first u ed rather elaborate laboratory studies were performed in order to avoid undesir able reactions As experience with the e agents has increased the e studies have become simplified When the hormones are administered systemically, weight and blood pressure should be checked daily and the fasting blood sugar should be determined at the onset of treatment and every four to six days thereafter The urine should be examined for evidence of glycosuria Eosinophil counts are taken as an index of the response to hormonal treatment *To compensate for a possible potassium loss 3 Gm of potassium chloride* daily are often given during the course of systemic hormonal therapy

Cortisone *Parenteral and Oral Administration* Cortisone is usually given in divided doses either parenterally or orally in a total dosage of 300 mg the first day and 200 mg the second thereafter 100 mg is given *daily for a 7- to 14-day* period and then *gradually tapered to a daily main*tenance do e of 20 to 50 mg The hormone is usually given twice daily if the parenteral method is selected or every six hours if administered orally At the conclusion of oral or parenteral cortisone therapy corticotropin is often given for two to three days to stimulate the adrenal cortex and thus overcome the depressant action of exogenous cortisone

In disease of the posterior ocular segment choroiditis endophthalmitis and generalized uveitis the parenteral or oral administration of cortisone (or the parenteral use of corticotropin) are definitely the methods of choice The effect of the two agents is about equal In patients who show no thera peutic response to intramuscular injections of corti one intravenous ad ministration of corticotropin is indicated

Cortisone and Hydrocortisone *Topical and Subconjunctival Administra tion* Most interesting for ophthalmologists is the topical administration of cortisone and hydrocortisone It has been shown by a number of investiga tors that cortisone applied topically to the eye has a therapeutic effect in anterior ocular diseases equal or superior to that obtained by parenteral injection This same local action has also been demonstrated experimentally The effect is noted within a few hours and is obviously independent of any general physiologic action Even when topical administration is prolonged for months no general physiologic reactions are observed only rarely is the eosinophil count affected even though the therapeutic effect may be marked Only small amounts of cortisone need be given topically to obtain the maximum therapeutic effect Topical use permits prolonged treatment requires no laboratory studies to avoid untoward effects and affords great economy

Olson and his associates[4] Steffensen and Kukora[3] have reported slight improvement in visual fields, visual acuity, and biophotometric readings in 9 of 14 patients receiving cortisone or corticotropin therapy parenterally However, an almost equal improvement was noted in 4 of 7 patients receiving intermedin a contaminant of corticotropin Except for these occasional cases, the results have been disappointing and a study of those in which improvement was noted yields no convincing evidence that there has been any true organic regression or inhibition of the degenerative disease When the fluctuations in vision visual fields and light sense, which occur under placebo treatment and even in untreated cases are considered together with the subjective emotional reactions of patients with a disease they are naturally reluctant to admit is hopeless it seems impossible to attribute the occasionally reported improvement to other than these factors Even though the slight improvement reported was causally related to hormonal therapy, continued parenteral therapy would probably be necessary to exert any sustained improvement Unless new and more convincing evidence is presented, it is probable that cortisone and corticotropin will take their place with other agents that have been used fruitlessly in the treatment of pigmentary degeneration of the retina

Fibrinoid Degeneration Fibrinoid degeneration of the connective tissue and myxomatous swelling of the ground substance are common to the various collagen diseases In the eye, the connective tissue system consists of cellular elements (fibroblasts) fibrillar elements (collagen reticulin, elastin), and an interfibrillary amorphous ground or cement substance (colloids hyaluronic acid, and mucopolysaccharides) The reaction of the connective tissue system to trauma be it physical bacterial or allergic may be either proliferative (keloid) or degenerative (fibrinoid degeneration) Other vascular and granulomatous changes of the various collagen diseases may differ but they all have the common denominator of fibrinoid degeneration with straightening and thickening of the fibers an increase in their optical refractivity and apparent friability In an excellent article, Stillerman[4] has reviewed the ocular manifestations of the various collagen diseases and has pointed out that vascular change and fibrinoid degeneration may account for both the systemic and the ocular findings In many of the ocular complications the connective tissue changes may be secondary, but in others such as scleromalacia perforans and the conjunctival nodules of erythema multiforme, they may be primary Stillerman then suggests that other ocular degenerative diseases of unknown etiology (Mooren's ulcer marginal corneal dystrophy keratoconus progressive myopia) may in truth represent a degeneration of the cellular, fibrillary or interfibrillary components of the connective tissue and like other collagen diseases be susceptible to the action of cortisone or corticotropin Duke Elder and his associates[3] have reported 3 cases of Mooren's ulcer treated with cortisone with questionable symptomatic improvement in 2 instances We have noted remarkable regression of rheumatic nodules of the sclera and some questionable improvement in early keratoconus, but there is as yet no evidence of

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The methods of parenteral administration of the adrenocortical hormones and corticotropin are well known In general the same methods are used in ophthalmic disease When cortisone and corticotropin were first used rather elaborate laboratory studies were performed in order to avoid undesirable reactions As experience with these agents has increased these studies have become simplified When the hormones are administered systemically weight and blood pressure should be checked daily and the fasting blood sugar should be determined at the onset of treatment and every four to six days thereafter The urine should be examined for evidence of glycosuria Eosinophil counts are taken as an index of the response to hormonal treatment To compensate for a possible potassium loss 3 Gm of potassium chloride daily are often given during the course of systemic hormonal therapy

Cortisone *Parenteral and Oral Administration* Cortisone is usually given in divided doses, either parenterally or orally in a total dosage of 300 mg the first day and 200 mg the second thereafter 100 mg is given daily for a 7- to 14-day period and then gradually tapered to a daily maintenance dose of 20 to 50 mg The hormone is usually given twice daily if the parenteral method is selected or every six hours if administered orally At the conclusion of oral or parenteral cortisone therapy corticotropin is often given for two to three days to stimulate the adrenal cortex and thus overcome the depressant action of exogenous cortisone

In disease of the posterior ocular segment choroiditis endophthalmitis and generalized uveitis the parenteral or oral administration of cortisone (or the parenteral use of corticotropin) are definitely the methods of choice The effect of the two agents is about equal In patients who show no therapeutic response to intramuscular injections of cortisone intravenous administration of corticotropin is indicated

Cortisone and Hydrocortisone *Topical and Subconjunctival Administration* Most interesting for ophthalmologists is the topical administration of cortisone and hydrocortisone It has been shown by a number of investigators that cortisone applied topically to the eye has a therapeutic effect in anterior ocular diseases equal or superior to that obtained by parenteral injection This same local action has also been demonstrated experimentally The effect is noted within a few hours and is obviously independent of any general physiologic action Even when topical administration is prolonged for months no general physiologic reactions are observed only rarely is the eosinophil count affected even though the therapeutic effect may be marked Only small amounts of cortisone need be given topically to obtain the maximum therapeutic effect Topical use permits prolonged treatment requires no laboratory studies to avoid untoward effects and affords great economy

Cortisone may be given as an ointment, or by subconjunctival injection, or by instillation as a collyrium Koff and his co workers [5] advocate sub conjunctival use on the grounds that an equal therapeutic effect is obtained, treatment is required only every one to three weeks and local reactions are reduced to the minimum On the other hand, Mosher[6] has reported distinctly poorer results with subconjunctival injection than with instillation of collyrium and Leopold and his co-workers[3] have reported mild but definite local reactions The latter studies on the permeability of the cornea to cortisone indicate no marked increase in absorption when cortisone is given by the subconjunctival route In our experience better results are obtained from instillation in the conjunctival sac slight though the trauma of subconjunctival administration may be it is avoided by instillation

If given as a collyrium the usual commercial preparation of cortisone which contains 25 mg per cc may be diluted 1 5 with saline thus reducing the 0 9 per cent concentration of benzyl alcohol which is used as a preserva tive, to a point where it produces little ocular irritation Merck and Co, Inc has specially prepared sterile ophthalmic suspensions in concentration *of 2 5 and 0 5 per cent in a buffered phosphate solution with suitable pre* servative This is almost entirely nonirritating and permits use of the collyrium in its full strength of 25 mg per cc if so desired, thus making frequent application unnecessary This strength, or a 1 2 dilution is usually *given every one to two hours during the acute stages of ocular inflammation* or until a satisfactory response is obtained thereafter the interval is length ened The eye is best kept under an eyepad to prevent the washing away of the insoluble steroid The maintenance dose usually is 1 drop every 12 hours

An especially convenient method for the topical application of cortisone is the use of an ophthalmic ointment which is now available It is easily applied by the patient permits slow and steady absorption obviates the need of an eyepad and avoids the loss of cortisone which is washed out by the tears and coagulates along the lashes when employed as a collyrium To avoid the competition of a mineral oil base in which cortisone is slightly soluble an aquaphor or lanolin base is used A concentration of 10 to 15 mg per Gm appears sufficient for the usual case although 25 mg per Gm may be indicated in acute cases A preparation containing 15 mg per Gm *(1 5 per cent)* is available commercially Preparations weaker than 10 mg per Gm appear to be ineffective Applied every three to four hours the thera peutic effect of the ointment is equal to that of the collyrium applied every hour The blurring of vision which results from use of an ointment is not usually troublesome because eyes requiring treatment throughout the day usually are so acutely inflamed that blurring of vision is not noticed, as maintenance therapy in noninflamed eyes the ointment need be used only once in 24 hours just before retiring Mention has already been made of the value of cortisone combined with an antibiotic in an ointment for the treat ment of external ocular infections

Hydrocortisone for parenteral administration has not been available long enough for its effect upon ocular disease to be tested extensively An

ointment and a collyrium have also been made available and there are two reports in the literature on the effect of topically applied hydrocortisone upon ocular inflammation Steffensen Ivy and Nagle [6] have reported 12 cases of anterior segment ocular disease treated with a hydrocortisone collyrium (5 mg per cc in 1 5 000 Zephiran) In 5 cases of iritis the results obtained with hydrocortisone were as good as those previously observed with cortisone and in one case better results were obtained with hydrocortisone Equally favorable action was observed in corneal ulcers vernal conjunctivitis allergic conjunctivitis phlyctenulosis and syphilitic interstitial keratitis No improvement was obtained in endothelial dystrophy

McDonald and his associates[27] recently reported that the results obtained in 46 cases of various anterior segment ocular diseases treated topically with hydrocortisone given either as a collyrium or by subconjunctival injection were equal or superior to those observed with topical cortisone They commented especially upon the antiphlogistic action and soothing effect of hydrocortisone as compared to cortisone They also noted specifically that when hydrocortisone was injected subconjunctivally vestiges of the crystals could be seen for two to three weeks Since it is less soluble in plasma and more slowly absorbed than is cortisone they believed smaller and less frequent dosage would be required Clinical use of hydrocortisone in the Wilmer Ophthalmological Institute has been limited to an ophthalmic ointment containing 15 mg per Cm (1 5 per cent) and a collyrium Our results coincide with those reported by Steffensen Ivy and Nagle [6] and McDonald et al [7] i e when used topically hydrocortisone appears as efficacious as cortisone Several cases that were resistant to topical cortisone notably a severe case of collagen disease of the sclera have yielded to topical hydrocortisone We can also confirm the antiphlogistic effect noted by McDonald and his co-workers

Topical use of cortisone or hydrocortisone either as an ointment or as a collyrium is the method of choice in all external diseases and in inflammation of the anterior ocular segment because it produces results equal if not superior to those of parenterally administered cortisone or corticotropin However if anterior uveal inflammation does not yield to topical therapy parenteral hormonal therapy should be tried Further when generalized uveitis or disease of the posterior ocular segment is once controlled by parenteral hormonal therapy the improvement can often be maintained with cortisone ointment

Corticotropin *Parenteral Administration* Corticotropin is given either by intramuscular injection or by intravenous infusion If intramuscular injection is the method chosen the initial dosage is usually from 80 to 120 units daily in divided doses It may be given in saline or in gel If given in saline the injections should be not less than six hours apart if the long acting corticotropin preparation is selected injections usually are given at 12 hour intervals After the first day the dosage may be increased maintained or decreased according to the therapeutic and eosinophil response If a favorable response is obtained the dosage is usually decreased from 120 units

daily to 80, then to 60 40, and finally 20 units, it should, however be increased again if an exacerbation of the ocular inflammation occurs Maintenance doses of 20 to 30 units daily or intermittent courses can be given over an extended period, provided the usual precautions are observed

When administered intravenously by glucose infusion, corticotropin is usually given over an eight-hour period, once daily This hormone is from 8 to 12 times as effective when given intravenously as when given intramuscularly, because its destruction by proteolytic enzymes of the muscle is avoided by the intravenous route For most conditions 20 units of corticotropin is the full daily intravenous dose required In ocular sarcoidosis or resistant sympathetic ophthalmia doses up to 40 units daily may be needed to elicit a satisfactory therapeutic response Again as a satisfactory result is obtained, the dose is gradually decreased over a 10- to 20-day period Intravenous corticotropin is indicated in patients with disease of the posterior *ocular segment, choroiditis endophthalmitis and generalized uveitis who* show either no therapeutic response to intramuscular injections of cortisone or corticotropin or no eosinophil response to the intramuscular corticotropin

In contrast to conventional methods of administering corticotropin parenterally for ocular disease Quinn and Wolfson[23] have recently recommended what they term *individualized intensive hormonal therapy* The principle of this therapy is that different individuals and different disease entities react in widely varying manners to these hormones Therefore dosage and duration of treatment are carefully adjusted to the patient s response If the disease entity does not react promptly to hormonal therapy, treatment is continued for a prolonged period again with careful adjustment of dosage to avoid overtreatment or untoward reactions Their patients were given adjuvant therapy (potassium salts, thyroid extract etc) to combat symptoms of hypercorticoidism which were found to occur in remarkably few patients with ocular disease In some cases treatment was continued for four to six months Long acting corticotropin was the hormone generally used When cortisone or intravenous corticotropin was used the equivalent dosage in long acting corticotropin was given in their report Thirty three patients with ocular disease were treated by this method A number had already been resistant to topical cortisone and the remainder were chiefly individuals whose prognosis was poor including several with changes usually considered irreversible (secondary optic nerve atrophy and degenerative changes in the choroid and retina) Many patients showed improvement only after prolonged therapy—some only after 30 to 175 days of treatment These authors obtained 29 successes or 80 per cent, in their series of 33 patients The patients with changes which are usually considered irreversible were among the successes As a possible explanation for the long delayed improvement the authors cite the work of Goldman and Richfield, [9] who reported the appearance of new junctional nevi in patients receiving long term treatment with either cortisone or corticotropin These junctional nevi were believed to be neuroepithelial structures composed of neuroepithelium and sensory nerves Quinn and Wolfson suggest that a

somewhat similar phenomenon may occur in the optic nerve and retina i e that prolonged treatment with cortisone or corticotropin may produce a proliferation of optic nerve or neuroretinal elements, or the sustaining components of such elements

Though it is undoubtedly true that the same disease—and different individuals—may react diversely to various methods of treatment so that the physician is justified in switching from cortisone to hydrocortisone or to long acting or intravenous corticotropin in resistant cases nevertheless on reviewing the results reported by Quinn and Wolfson it appears that their conclusions of a long-delayed response to adjusted corticotropin therapy are not entirely justified For example Table 27 shows that 11 of their patients

Table 27

ANALYSIS OF FINDINGS OF QUINN AND WOLFSON[25]

Disease	*No of Patients*	*Average Days of Treatment*	*Corticotropin Units* Average			*Results*		
			Maximum Daily Dose	Daily Dose	Total Dose	Excellent	Good	Poor
Acute monosymptomatic retrobulbar neuritis	5	24	51	25	492	4	1	0
Acute angiospastic retinopathy	2	13	78	61	50	1	1	0
Acute recurrent iridocyclitis (refractory to topical cortisone)	4	29	44	38	802	4	0	0
Totals	11	22	61	31	681	9	2	0

received what might be termed conventional treatment (a total equivalent dosage of 681 units of corticotropin given for an average of 22 days) with excellent results in 9 patients and remission in 2 There is nothing unusual in these findings Table 28 on the other hand shows the results in 22 of their patients in whom the average duration of treatment was 80 days, the average maximum daily dose 151 units the average daily dose 78 units and the average total dose 5 470 units In this group excellent remission was reported in 11 patients good remission in 8 and poor results in 3 At first glance this is impressive However 15 of these had acute or chronic uveitis and the average time for attainment of the therapeutic change was 65 days in 7 patients 177 days were required The results obtained were excellent in 7 of the 15 patients good in 6 and poor in 2 In any 15 cases of acute or chronic uveitis treated for periods varying from 39 to 177 days a spontaneous remission in 7 and improvement in 6 patients would not be an unusual outcome irrespective of therapy

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Disease	No of Patients	Average Days of Treatment	Corticotropin Units — Average: Maximum Daily Dose	Daily Dose	Total Dose	Results: Excellent	Good	Poor
Acute monosymptomatic retrobulbar neuritis	5	21	51	25	492	4	1	0
Acute angiospastic retinopathy	2	13	78	61	750	1	1	0
Acute recurrent iridocyclitis (refractory to topical cortisone)	4	29	44	38	802	4	0	0
Totals	11	22	61	31	681	9	2	0

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The results in 7 cases of retrobulbar neuritis are scarcely more impressive Four of these are described as acute optic neuritis of unknown etiology of from two days to three weeks' duration when treatment was started The remission obtained was excellent in 2 patients "good" in 1 and "poor" in the fourth In view of the tendency of many cases of optic neuritis to subside spontaneously in a few weeks, these findings certainly are not remarkable

Table 28

ANALYSIS OF FINDINGS OF QUINN AND WOLFSON[28]

Disease	*No of Patients*	*Average Days of Treatment*	*Corticotropin Units*			*Results*		
			Average					
			Maximum Daily Dose	Daily Dose	Total Dose	Excellent	Good	Poor
1 Uveitis								
Acute or chronic recurrent disseminated chorioretinitis	7	177	154	57	9148	5	1	1
Acute or chronic chorioretinopathy (specific etiologic variants)	3	46	142	82	3872	0	2	1
Acute nonrecurrent chorioretinitis	2	65	82	54	3820	2	0	0
Chronic inflammatory anterior segment disorder (resistant to topical cortisone)	3	39	130	90	2693	0	3	0
2 Optic Neuritis								
Acute optic neuritis etiology unknown	4	36	191	94	3376	2	1	1
Acute or chronic retrobulbar neuritis known etiology	3	116	208	94	9910	2	1	0
Totals	22	80	151	78	5170	11	8	3

The results in 3 of the cases of retrobulbar neuritis of known etiology require more consideration One patient with neuromyelitis optica of seven days duration and total blindness in each eye when treatment was started recovered to 20/30 vision after five months Such recovery is not usual but certainly in every *large clinic remarkable recovery of* vision in neuromyelitis optica is frequently observed In the second case (retrobulbar neuritis from disseminated sclerosis of one year's duration apparently with some visible

optic nerve atrophy already present) a recovery to 20/20 vision in three months was unusual but again it is well known that remissions and exacerbations are characteristic of disseminated sclerosis and more evidence than that presented would be required before the improvement could be attributed to the hormonal treatment The last case of syphilis induced retrobulbar neuritis of three months duration improved to 20 60 vision in two and one half months—a result which would be expected Finally it would require the most minute study of the individual case and all possible factors involved before the conclusion could be accepted that organic optic nerve atrophy and retinal degeneration have been reversed by hormonal therapy

Effect of the Adrenocortical Hormones upon Ocular Reactions and Disease in Experimental Animals

Despite extensive investigations by immunologists clinicians physiologists and chemists the mechanism whereby the adrenocortical hormones and corticotropin exert their dramatic effect upon inflammation is as yet undetermined However certain observations have been made of their effect upon experimental ocular reactions and disease which throw considerable light on their mode of action and are of particular interest to clinical ophthalmologists Such observations are based upon studies of ocular inflammations caused by various hypersensitivity reactions irritants and infections the capillary permeability of the eye wound healing and neovascularization of the cornea the development of the ocular granulomatous lesions of tuberculosis and brucellosis the absorption of cortisone in the eyes and the possible role of cortisone and corticotropin in the pathogenesis of diabetic retinopathy These studies may be summarized as follows

Ocular Inflammation ***Inflammation Due to Hypersensitivity Reaction*** The three recognized anaphylactic and allergic reactions which can readily be evoked in the eyes of experimental animals are

(1) The anaphylactic reaction due to sensitization and intoxication with protein agents horse serum being the protein commonly used This was first described by Nicolle and Abt[33] in 1908 After sensitization of the animal has been accomplished by the proper systemic injection of horse serum the injection of small amounts of horse serum in the anterior chamber produces an intense nongranulomatous iritis characterized histologically by edema and lymphocytic infiltration of the uveal tract This iritis is transient lasting for four days or more and then usually subsiding without residue

(2) The allergic ophthalmic reaction due to sensitization and intoxication with bacterial antigens This was first described by Derick and Swift[34] in 1929 In the form most commonly used the animal is sensitized by repeated intracutaneous injections of living alpha streptococci or killed beta streptococci After sensitization injections of minute quantities of the specific homologous antigen in the anterior chamber produces a nongranulomatous iritis of some 3 to 14 days duration In highly sensitized animals this may be accompanied by clouding and vascularization of the cornea

(3) The focal reaction to tuberculin shown by eyes with tuberculous

The results in 7 cases of retrobulbar neuritis are scarcely more impressive Four of these are described as acute optic neuritis of unknown etiology of from two days' to three weeks' duration when treatment was started The remission obtained was excellent in 2 patients "good" in 1, and poor' in the fourth In view of the tendency of many cases of optic neuritis to subside spontaneously in a few weeks these findings certainly are not remarkable

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(3) The focal reaction to tuberculin shown by eyes with tuberculous

disease after the systemic injection of an excessive dose of tuberculin This reaction has long been recognized clinically It was produced and described in experimental animals by Woods and Burky[3] in 1943 If immune allergic rabbits with a restrained secondary ocular tuberculosis are given a systemic injection of 100 mg of old tuberculin, within 24 to 48 hours the quiescent, diseased eyes flare up with a typical nongranulomatous iritis which persists for 2 to 7 days and then fades

It was found that when sensitized animals in these three categories were treated with parenteral cortisone or corticotropin for a four-day period prior to the anterior chamber injections and for a four-day period afterward, the ocular reactions were partially or completely suppressed, the injected eyes of the treated animals showing either a minimal or no reaction to the injection of the specific antigen or to the parenteral injection of tuberculin It was further found that, if cortisone or hydrocortisone was injected into the anterior chambers at the same time the specific antigen was given, the reaction could be suppressed by this means alone The degree of suppression shown after either parenteral or topical treatment was proportional to two *factors—the amount of the hormone given and the degree of hypersensitivity* shown by the experimental animal In these various experiments cutaneous reactions to horse serum, alpha or beta streptococci or tuberculin were likewise partially or completely suppressed by parenteral administration of cortisone or corticotropin However the underlying tissue hypersensitivity was not disturbed, for when treatment was discontinued and either the eyes or the skin of the sensitized animals were later reinjected with the specific antigen they reacted quite as briskly as the untreated controls

Inflammation Due to Irritants In 1931 Seegal and Seegal,[33] in the course of experiments on local tissue hypersensitivity showed that introduction into the anterior chamber of such irritants as glycerin iodine etc produced a transient iritis A similar iritis can also be produced by staphylococcus toxin and a more intense iritis which may actually be accompanied by corneal necrosis and perforation of the globe can be produced by jequirity[34] If the animals were parenterally treated with cortisone or corticotropin four days prior to and five days after the anterior chamber injection the iritis produced by glycerin or staphylococcus toxin could be completely inhibited A similar suppression was observed when the test animals were treated with cortisone injected in the anterior chamber synchronously with the irritant Again it was found that the degree of suppression, from mild to absolute, was quantitatively related to the amount of the hormone administered

When jequirity infusions were used, if the infusion was sufficiently strong to produce necrosis neither the parenteral administration of cortisone or corticotropin nor the anterior chamber injection of cortisone had any effect upon the resulting lesions[34] When weaker infusions were used the inflammation shown by the controls was partially or completely suppressed by parenteral cortisone or corticotropin and by topical cortisone or hydrocortisone The degree of suppression varied with the degree of the insult i e, with the strength of the jequirity infusion used

Inflammation Due to Infection In studying the suppression of the focal reaction to tuberculin by the parenteral administration of cortisone it was found that when the cortisone was continued for three weeks after the focal reaction in the eye had subsided, the eyes of the treated rabbits became white and free of visible inflammation although the tubercles on the iris continued unchanged or even increased slightly Thus for a short period treatment with cortisone produced the peculiar picture of white noninflamed eyes with an active tuberculosis [35]

In investigating the effect of hormonal therapy upon the development of ocular tuberculosis it was found that parenteral administration of cortisone hydrocortisone or corticotropin suppressed all inflammation in the inoculated eyes for a period of five to six weeks During this period the organisms quite evidently propagated for myriad tubercles later developed after this prolonged incubation period and the lesions were found to be swarming with bacilli It thus appeared evident that in these experimental animals the adrenocortical hormones and corticotropin inhibited the inflammatory reaction due to infection with the Mycobacterium tuberculosis Studies as yet unreported indicate that this suppression of the inflammation of infection is not limited to tuberculosis but occurs in the granulomatous uveitis produced by Brucella organisms

From this group of experiments it was concluded that the ability of cortisone, hydrocortisone and corticotropin to control inflammation was not restricted to the inflammatory response secondary to hypersensitivity reactions but extended to that produced by irritants and by infection Since small amounts of cortisone injected in the eye immediately suppressed the inflammatory response produced either by the hypersensitivity reaction or by irritants, the hormone apparently acted locally at the cell level and its action was independent of any general physiologic change It appeared clear that these agents did not affect the underlying antigen antibody reaction but in some unexplained way shielded the cells lessened the toxic effect of the allergic reaction of the irritant or of the bacterial toxin and so prevented the inflammatory response It was also evident that the ability of these hormones to control inflammation was only relative and failed in the presence of too powerful an insult

Capillary Permeability If a decrease in capillary permeability were produced by cortisone or corticotropin such action would go far in explaining the inhibitory effect of these hormones upon inflammation and exudation Various studies in collagen disease[36] indicate that capillary fragility as tested by suction devices is decreased in these diseases after cortisone or corticotropin therapy Similarly Armstrong and Irons[37] reported studies on the protein content of the vesicles in a patient with scleroderma which indicated that after treatment with cortisone or corticotropin the protein content of the vesicles fell markedly approaching that of a transudate This they interpreted as evidence of a decrease in capillary permeability

Two methods have been employed to determine the permeability of the capillaries of the eye, the first being to assay the passage of protein across

the ciliary blood aqueous barrier and the second, to assay the passage of fluorescein

It is well known that in normal animals after repeated punctures of the anterior chamber the regenerated aqueous has a much higher protein content than the original aqueous indicating an increase in permeability of the capillaries at the ciliary barrier Irvine and Irvine[38] studied the protein content of the first and second aqueous of normal animals under treatment with cortisone and found that the increased protein content of the *second aqueous was not affected by such treatment They concluded that* in the normal rabbit under the conditions of their experiment, cortisone had no effect upon capillary permeability

The action of cortisone in inhibiting the passage of fluorescein across the ciliary blood aqueous barrier was first studied by Leopold and his associates[5] They found that treatment of a normal animal with cortisone had no inhibitory effect upon the passage of intravenously injected fluorescein into the aqueous indicating that such treatment did not decrease the permeability of the capillaries of a normal rabbit for molecules the size of fluorescein McDonald et al[7] have recently confirmed this finding for hydrocortisone showing that prior *subconjunctival injection of hydrocortisone* did not inhibit the passage of fluorescein into the aqueous of the normal eye

Cook and MacDonald[39] concluded from their study of patients that treatment with cortisone did not influence or decrease the passage of fluorescein into the anterior chamber of noninflamed eyes However in eyes inflamed from various ocular diseases where the passage of fluorescein in the anterior chamber was greatly increased treatment with cortisone reduced the passage of fluorescein to the level shown by noninflamed eyes They concluded that though cortisone had no effect upon the capillary permeability of the normal human eye it played an important role in reducing the increased capillary permeability associated with inflammation This agrees with Biegel s observation[18] that in anaphylactic uveitis produced by sensitization and intoxication with horse serum cortisone had a marked inhibitory effect on the exudation However McDonald et al[7] have recently reported an experiment in rabbits in which prior subconjunctival injection of hydrocortisone and prior subconjunctival and systemic injections of cortisone had no inhibitory effect upon the passage of streptomycin into the aqueous of a previously inflamed eye Further investigation of this important question is in order

Wound Healing The general studies of Ragan et al[40] and Spain Molomut and Haber[41] clearly indicate that treatment of the experimental animal with cortisone interferes with new fibroblast formation but not with granulomatous tissue already formed The evidence of *an effect upon epithelization* is somewhat conflicting The question of wound healing in the eye has been especially investigated[3, 42-44] Friedenwald[4] studied the effect of treatment with cortisone upon the mitosis rate of corneal epithelium in rats and found no difference between the treated *and the control animals*

Leopold and his associates[9] found that rabbits treated with cortisone showed slight delay in epithelization of the cornea after standard trephine wounds Though they observed no gross clinical difference in the healing rate of stromal wounds in the treated and control rabbits nevertheless histologic studies showed definitely less granulomatous tissue in the treated eyes than in the controls They made no observations on endothelial regeneration

Newell and Dixon[43] studied the effect of subconjunctivally injected cortisone upon the healing of full corneal grafts and found no evidence that cortisone had any significant influence on the normal rapid proliferation of corneal epithelium A marked difference in stromal healing was noted In the untreated controls leukocytes and eosinophils began to disappear after the third day and proliferating keratoblasts migrated between the wound margins displaced the epithelium and formed cellular connective tissue In the treated eyes leukocytes persisted up to the eighth day Keratoblastic proliferation was minimal and as late as the eleventh day the wound was filled only with epithelium and fibrin They noted that endothelial cells in the grafts were absent in many sections and were fragmented in others and that fibrin filled the posterior edges of the wound

Ashton and Cook[44] investigated the effect of cortisone upon perforating corneal wounds In an exceptionally well illustrated paper they showed that cortisone inhibited the fibrinous coagulum cellular infiltration and fibroblastic repair Like Newell and Dixon they observed fragmentation of the endothelium and inhibition of endothelial regeneration The inhibition of both stromal and endothelial repair was related to the quantity of cortisone administered It was moderate with small doses when repair was still adequate but marked with large doses when repair might be completely inhibited McDonald and his associates [7] have found these findings to hold true for hydrocortisone reporting a similar inhibition of stromal repair in the treated eyes

Just how cortisone inhibits the fibroblastic reaction is a mystery Steen[45] in a recent study found that cortisone when added to tissue cultures in concentrations up to 25 times that of the usual therapeutic levels had no effect whatsoever upon the fibroblastic growth of chick embryos

It is doubtful however if these well established experimental findings have any marked clinical significance Ashton and Cook[44] do not state the amount of cortisone that was required to obtain complete inhibition of repair It is quite probable that the amount so administered was well in excess of that usually given clinically *Certainly both general surgeons and ophthalmologists have repeatedly operated on patients under cortisone or corticotropin therapy and consistently have observed no undue retardation in the healing of cutaneous or corneal wounds*

Neovascularization In 1950 Jones and Meyer[46] reported that cortisone applied topically had a marked inhibitory action on the neovascularization which so regularly followed caustic burns of the cornea Quite recently this finding has been fully confirmed by Ashton Cook and Langham[47] and also by Lister and Greaves [48] Ashton and his associates determined the effect of

both subconjunctivally and parenterally administered cortisone upon the vascularization and corneal edema produced by injection of a solution of alloxan into the anterior chamber They found that such injections of cortisone reduced and delayed neovascularization but did not completely inhibit it The degree of inhibition was much greater when cortisone was administered subconjunctivally Similarly they found that cortisone given subconjunctivally markedly inhibited edema opacification and the increased thickness of the cornea but given parenterally it had no such effect Lister and Greaves[48] found that cortisone administered either subconjunctivally or parenterally inhibited the vascularization secondary to thermal burns of the cornea These findings have been confirmed by McDonald and his associates for cortisone and for hydrocortisone [7]

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Granulomatous Ocular Lesions ***Tuberculosis*** There is considerable evidence that treatment of experimental animals with cortisone may radically alter the course and possibly the pathogenesis of systemic tuberculous lesions First *Michael Cummings and Bloom* [49] and then *Spain Molomut* and Haber[41] reported experiments which indicated that treatment with cortisone depressed the natural resistance to infection possessed by tuberculosis resistant rats Later Lurie and his co-workers[50] showed that in rabbits with pulmonary tuberculosis produced by inhalation of bacilli the whole course of the ensuing lesions was radically altered by cortisone treatment with caseous foci in the tubercles and a great increase in the numbers of the bacilli in the lesions A series of recent experiments[51] indicates that in the eye the entire course and type of tuberculous lesions can be altered for the worse by treatment of the animals either with topically or parenterally administered cortisone or parenterally administered hydrocortisone These findings were, in brief as follows

Ocular tuberculosis runs a radically different course in normal and in immune-allergic rabbits In the normal nonimmune rabbit there is a minimal reaction to injection of tubercle bacilli into the anterior chamber The incubation period thereafter is followed by the development of hard tubercles A high degree of reactivity to tuberculin and with this a stage of acute inflammation then develop in the diseased eye Next the tubercles soften necrosis and caseation follow the eyes go into buphthalmos and within six to eight weeks the majority rupture On histologic examination the eyes show large caseous tubercles with tissue destruction In immune allergic rabbits the picture is radically different An initial inflammatory reaction to the tuberculoprotein in the inoculum fades in three to seven days There is then an incubation period of varying time after which the eyes develop a restrained tuberculous disease Acute inflammation necrosis caseation buphthalmos and rupture of the globe are rarely if ever observed Within three to five months the condition of the eyes becomes quiescent, and variable residual

scarring is present On histologic examination only minimal healed granulomatous lesions are found

In immune-allergic rabbits which for a 30- to 58-day period from the time of inoculation were given cortisone either parenterally or topically or hydrocortisone parenterally the development of visible lesions was inhibited for 20 to 48 days while the controls developed lesions in 10 to 14 days After this prolonged incubation period the eyes of the treated animals developed lesions similar to the controls When treatment was then stopped after 30 to 58 days the eyes underwent acute exacerbations and as early as three days after termination of treatment showers of soft tubercles developed on



FIG 39 Ocular tuberculosis in untreated normal rabbit 30 days after inoculation illustrating advanced caseous tuberculosis buphthalmos and impending rupture of globe (From Woods and Wood [51])

the iris and in the cornea On bacterial stains these were found to be swarming with bacilli Thereafter the eyes developed necrosis caseation and buphthalmos and some of them ruptured The whole picture of the disease was radically changed and the eyes of the immune allergic rabbits assumed the same clinical and histologic pattern as that observed in normal nonimmune rabbits It is also noteworthy that in this experiment the cortisone treated rabbits remained in good condition and showed no undue mortality rabbits treated with hydrocortisone however were found to have a marked loss in body weight high blood sugar glycosuria and a high mortality The important features of these experiments are shown in Figures 39 to 43

Study of the animals indicated that this changed picture in the immune allergic rabbits was not caused by loss of their immune status but probably was related to inhibition of phagocytosis and fibrosis and possibly to depression of the adrenal cortex by the cortisone with consequent adrenocortical hormone deficiency when exogenous cortisone was withdrawn Immune-allergic rabbits similarly treated with corticotropin did not develop this

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FIG 39 Ocular tuberculosi in untreated normal rabbit 30 day after inoculation illu trating advanced caseous tuberculosi buphthalmos and impending rupture of globe (From Wood and Wood [1])

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Granulomatous Ocular Lesions. *Tuberculosis.* There is considerable evidence that treatment of experimental animals with cortisone may radically alter the course and possibly the pathogenesis of systemic tuberculous lesions. First Michael, Cummings and Bloom[49] and then Spain, Molomut and Haber[41] reported experiments which indicated that treatment with cortisone depressed the natural resistance to infection possessed by tuberculosis-resistant rats. Later Lurie and his co-workers[50] showed that in rabbits with pulmonary tuberculosis produced by inhalation of bacilli the whole course of the ensuing lesions was radically altered by cortisone treatment, with caseous foci in the tubercles and a great increase in the numbers of the bacilli in the lesions. A series of recent experiments[51] indicates that in the eye the entire course and type of tuberculous lesions can be altered for the worse by treatment of the animals either with topically or parenterally administered cortisone or parenterally administered hydrocortisone. These findings were in brief as follows.

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Fig 39 Ocular tuberculosis in untreated normal rabbit 30 days after inoculation illustrating advanced caseous tuberculosis buphthalmos and impending rupture of globe (From Wood and Wood [51])

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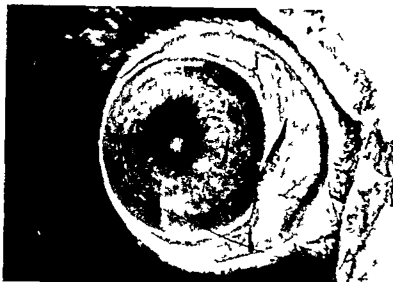


Fig 40 Ocular tuberculosis in untreated immune allergic rabbit 90 days after inoculation illustrating restrained self limited disease (From Woods and Wood [51])

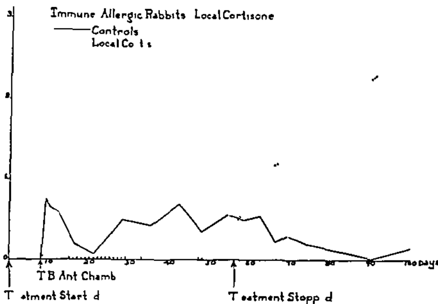


Fig 41 Graph illustrating the course of ocular tuberculosis in untreated immune allergic rabbit (solid line) and immune allergic rabbit treated topically with cortisone (dotted line) Note suppression of initial allergic reaction suppression of all inflammation for 48 days and violent rebound phenomenon 3 days after termination of treatment (From Woods and Wood [51])

changed picture of tuberculous disease A possible explanation for the failure of corticotropin treated rabbits to develop this rebound phenomenon may be that such rabbits maintained their adrenal hypertrophy for the 100 day period of observation after cessation of treatment and thus probably were not deprived of the protective influence of their own cortisone



FIG 42 Showers of soft tubercles on iris of immune allergic rabbit treated topically with cortisone occurring 3 to 11 days after cessation of treatment (From Woods and Wood [41])



FIG 43 Final appearance of eye of immune allergic rabbit treated topically with cortisone 30 days after termination of treatment Compare with Figures 39 and 40 and note transformation of process from restrained healing disease to fulminating caseous disease (From Woods and Wood [41])

These findings with respect to ocular tuberculosis are in accord with those of others who investigated systemic tuberculosis and in general are similar to the observations of Turner and Hollander[52] in a study of experimental syphilis in rabbits When such rabbits were treated with cortisone these investigators found that the animals developed large, boggy, nonulcerative

lesions (which were swarming with treponemata), instead of the usual circumscribed lesions observed in the untreated controls. A sharp rebound phenomenon occurred on cessation of treatment with spread and violent accentuation of the disease.

These experiments appear to have particular clinical significance. *Unless it can be proved later that streptomycin and p-aminosalicylic acid or such other newer agents as Nydrazid when given concurrently with cortisone will prevent these recurrences and rebound phenomena in tuberculous eyes, it would be wise to assume that cortisone therapy should be severely restricted in any case of proved or suspected ocular tuberculosis.*

Brucellosis. As yet unreported experiments from the Wilmer Institute indicate that hormonal therapy *may have an untoward action in ocular brucellosis.* Immune allergic rabbits (animals with a previously induced systemic Brucella infection) were used in these experiments, the ocular lesions being produced by a later anterior chamber injection of Brucella organisms after the immune status had developed. It was found that the initial allergic ophthalmic reaction which occurred regularly in the untreated controls was completely or partially suppressed by the parenteral injection of cortisone, hydrocortisone or corticotropin and by the topical application of cortisone ointment. Thereafter, clinical evidences of minor ocular infection and inflammation were fewer. The incidence of severe ocular infection, however, was undiminished and an increased susceptibility of the eyes to a smaller inoculum was observed. Moreover, the severity of the lesions in the reacting eyes appeared enhanced by the continued hormonal treatment. No rebound phenomena such as were constantly observed in tuberculous eyes occurred in these rabbits. It was concluded that under the conditions of this experiment *the adrenocortical hormones and corticotropin were of no value in the* treatment of experimental ocular brucellosis except to suppress the minor inflammation and infection which in the control eyes subsided spontaneously. Hormonal therapy appeared to be contraindicated in that it rendered the eyes of some animals more susceptible and increased the severity of the infection in the reacting eyes.

No definitive explanation of the mechanism of such an action has as yet been found, although it has been suggested that inhibition of the minor inflammation or infection may have inhibited local phagocytosis of the injected organisms. It is of interest that in this experiment the cutaneous reactivity of the chronically infected animals to brucellergin was either completely suppressed or greatly diminished.

Absorption of Cortisone by the Eye. When the effect of topical cortisone upon ocular inflammation was first observed, it was difficult to understand just how a substance as insoluble as cortisone acetate could be absorbed from the conjunctival sac. That it did penetrate into the eye was clearly attested by its effect upon nongranulomatous iritis. Leopold and his co-workers[3] studied the question experimentally and analyzed the aqueous for its cortisone content after instillation of cortisone suspension into the conjunctival sac and after both *subconjunctival and retrobulbar injections.* They found

that all methods of application resulted in penetration of cortisone into the aqueous and that subconjunctival injection was only slightly superior to instillation of the collyrium in the conjunctival sac.

In the course of experiments on the effect of topically applied cortisone upon the various hypersensitivity reactions, we noticed a curious phenomenon. After the anterior chamber injection, the chalky crystalline suspension of the cortisone acetate was clearly visible as a flocculent mass. Within 24 to 36 hours all trace of it had disappeared, while corticotropin in the anterior chamber was slowly absorbed over a period of several days. However, when cortisone acetate was given subconjunctivally, the crystals were readily seen beneath the conjunctiva for a period of approximately a week. It seemed probable that cortisone in the anterior chamber or in the conjunctival sac underwent some chemical alteration which made it readily soluble and easily absorbed. Just what this change was is a complete mystery, although a recent observation by Steen[45] may be important. In the course of his experiments on the growth of mesoderm in tissue cultures with cortisone, he observed that in the presence of living cells the insoluble cortisone acetate combined with glucose to form a new and soluble compound which may be cortisone glucoside. The similarity of cortisone in the anterior chamber of a living eye to the conditions of Steen's experiments is striking. Perhaps he has found an answer to the puzzling question of absorption of cortisone by the eye. Certainly it is an interesting field for further investigation.

Possible Role of Adrenal Cortex in the Pathogenesis of Diabetic Retinopathy. Recent and as yet preliminary reports of investigations suggest that the adrenocortical hormones and corticotropin may play a significant role in the pathogenesis of diabetic retinopathy. The present status of these investigations may be summarized as follows.

Dana, Eversole and Zubrod[13] reported a clinicopathologic study of 190 diabetic patients autopsied in The Johns Hopkins Hospital between 1938 and 1950. These patients fell into two rather sharply divided groups. The first group of 57 patients showed the typical Kimmelstiel-Wilson aneurysms in the glomeruli of the kidneys; 90 per cent of these showed typical aneurysmal capillary lesions in the retina—the basic picture of diabetic retinopathy. In studying the histories of the patients in this group, it was conspicuous that none had shown any evidence of acidosis and that in the absence of exogenous insulin none had developed ketosis. The second group of 133 patients did not have Kimmelstiel-Wilson lesions in the glomeruli of the kidneys. Only 10 per cent of this group showed capillary aneurysms in the retina. Insulin deficiency, acidosis, and ketosis were prominent findings.

On the basis of this study, the authors suggested that Kimmelstiel-Wilson glomerular aneurysms and diabetic retinopathy are part of the same clinical entity; that they are not related to an insulin deficiency, but rather that the diabetes in these patients is the result of excess of the hyperglycemic glycogenolytic factor, and that this factor may be responsible for the vascular capillary lesions. There was suggestive evidence that the alpha cells

of the pancreas may be concerned in the excess of the hyperglycemic glycogenolytic factor

It is also pertinent that these Kimmelstiel-Wilson lesions in the glomeruli have been observed in experimental animals under prolonged cortisone and hydrocortisone treatment that the development of retinal aneurysms has been observed in patients under prolonged corticotropin therapy and that Kimmelstiel Wilson lesions have been found in the glomeruli of one such patient at autopsy [54] There are also a number of reports of a diabetic retinopathy developing from mild diabetes during the course of a pregnancy with spontaneous and complete regression of the retinopathy following delivery These various clinical and histologic observations suggest the possibility that the adrenocortical hormones may play some part in the pathogenesis of diabetic retinopathy

Stimulated by these various observations Becker[54] has undertaken a clinical and experimental investigation of the possible role of adrenocortical hormones and corticotropin in the pathogenesis of diabetic retinopathy This investigation is still in its early stages but the preliminary reports are most interesting It was first found that rabbits made diabetic with alloxan did not develop either a retinopathy or Kimmelstiel-Wilson lesions in the glomeruli However when the animals were given prolonged treatment with corticotropin distortion of the capillary pattern and definite capillary aneurysms developed in the retina together with Kimmelstiel Wilson lesions in the glomeruli of the kidney The investigator then directed his attention to a study of the adrenals of diabetic patients autopsied in The Johns Hopkins Hospital Although the weight of the adrenals is admittedly a poor method of evaluating adrenal activity nevertheless the adrenals of the Kimmelstiel Wilson retinopathy group were found to be 24 per cent larger than those of the controls who had diabetes without retinopathy The Kimmelstiel-Wilson retinopathy group also showed a great increase in lipid laden vacuolated cells in the zona fasciculata of the adrenals An effort to explain these striking differences on the basis of the immediate cause of death stress factors etc was unsuccessful and the author believed that the evidence of increased adrenocortical activity found in the Kimmelstiel-Wilson retinopathy group was related to the pathogenesis of the lesions On the basis of these and other observations he has advanced the working hypothesis that, in addition to the pancreatic lesions pituitary stimulation with the result int liberation of excessive amounts of corticotropin and increased production of adrenocortical steroids are factors in the development of both diabetic retinopathy and Kimmelstiel Wilson lesions in the kidney

Obviously these investigations are all in the preliminary stage and more experimental proof will be required to establish this hypothesis Nevertheless its attractiveness is undeniable It affords an explanation for many established clinical observations which heretofore have been inexplicable It opens possibilities of a therapeutic approach to a disease for which there has until now been no therapy whatsoever For example Green et al [55] have reported a case of diabetic retinopathy in which bilateral adrenalectomy was

done and the patient was maintained thereafter on cortisone, with regression of the retinopathy. The possibility that corticotropin and the adrenocortical steroids may play a significant role in the pathogenesis of diabetic retinopathy may also dampen the enthusiasm of the many investigators who have tried hormonal therapy in this disease.

Contraindications to the Use of Adrenocortical Hormones in Eye Diseases

When cortisone and corticotropin were first used clinically a great mass of information on their general physiologic action had already been accumulated. It was well known that prolonged clinical use of either hormone might produce such untoward physiologic effects as retention of salt and water with a resulting hypertension, relatively insulin resistant hyperglycemia, Cushing's syndrome with the characteristic facies, hirsutism, and amenorrhea, and alteration in cerebral function. Their use therefore was contraindicated in patients with hypertension, nephritis, diabetes, and various psychoses.

As further clinical and experimental information was gathered it was found that in addition to their unexplained action on collagen diseases they had an inhibitory effect upon inflammation, exudation, neovascularization and fibroblastic reaction, and various warnings and speculations were advanced concerning their final effect in certain infectious diseases. Thus Armstrong and Irons[37] warned that "when the inflammatory reaction has a defensive action, that is, when infection exists in the inflamed tissue, the action of ACTH and/or cortisone can be clearly deleterious." Similarly, in the discussion of the paper by Olson et al.[4] Swan stated, "Much remains to be determined about the dosage and side effects, and the possibility of delayed or indirect effects has scarcely been investigated." The validity of these warnings is now becoming apparent.

In deep infections of the cornea and in granulomatous disease of the uveal tract, the essence of resistance or healing is first bacteriostasis with immobilization of the invading organisms, followed either by their destruction through phagocytosis or their encapsulation by a fibroblastic reaction. The final tissue repair is by fibrosis. When cortisone and corticotropin suppress inflammation they do so irrespective of whether the inflammation is caused by the hypersensitivity reaction, irritants, or infection. In suppressing the inflammation secondary to infection, the accompanying mobilization of phagocytic cells and fibroblasts is likewise suppressed, and the fibroblastic reaction and neovascularization are impaired. Thus in experimental ocular tuberculosis the suppression of phagocytosis and fibrosis by cortisone appears to be intimately concerned in the reversal of the picture from a restrained process to a destructive one.

Is there any evidence that inhibition of neovascularization, fibrosis and phagocytosis by hormonal therapy has an adverse effect in human ocular disease? At a meeting of the Study Section of the National Institutes of Health and the American Venereal Disease Association in Washington, D.C., in April 1951, it was clearly brought out by a number of clinicians that when

cortisone was given during the early stages of the interstitial keratitis of congenital syphilis, its use was followed by prompt relief of all inflammation clearing of the interstitial corneal infiltrates and prevention of the vascularization phenomenon These immediate results in early cases are incontestable However if the keratitis has advanced to the stage of corneal necrosis before treatment is started the use of cortisone has little or no effect A study of some of the early successfully treated cases indicates that prolonged therapy may be necessary to prevent immediate recurrence In the Wilmer Institute series are several cases which have been under treatment with topical cortisone for a year or longer While under treatment the eyes remain white and free of inflammation but if a minimum of treatment is stopped within 72 hours the eyes again exhibit evidences of returning inflammation Experimental studies[56] have shown that an immunity of the cornea to reinoculation with Treponema pallidum accompanies the development of the vascularization cycle and it has been suggested that the vascularization per se is responsible for such immunity Therefore it may well be that the inhibition of vascularization in the cornea in interstitial keratitis is not desirable from the viewpoint of actual healing or prevention of recurrences *Indeed there is doubt in the minds of many syphilologists and ophthalmologists[57] whether cortisone therapy in interstitial keratitis is justifiable*

Mention has already been made of the high incidence of recurrences of granulomatous uveitis after apparent primary control of the disease with cortisone or corticotropin In many of these cases there is a notable absence of the usual glial scars It is well recognized that a large percentage of such granulomatous uveitis is tuberculous various investigators placing the incidence at 10 to 40 per cent while some German authorities believe it is still higher It may well be that many of the recurrences of granulomatous uveitis observed in tuberculous eyes after the termination of hormonal therapy are rebound phenomena such as occur in experimental animals As yet no histologic material from patients is available for study to confirm this supposition Clinical evidence however lends support to the idea that such rebound phenomena do occur in human beings Two patients have been treated in the Wilmer Institute for undoubted tuberculous choroiditis all the criteria necessary for such a diagnosis being fulfilled in both cases Both of these patients received intensive treatment with cortisone to control the choroidal inflammation and exudation while at the same time they were given streptomycin with either Promizole or p aminosalicylic acid as the adjuvant Cortisone was continued for the usual period and the streptomycin and adjuvant therapy was given for 42 to 60 days In both cases immediate satisfactory circumscription of the exudates and clearing of the vitreous were obtained with later resolution and disappearance of the exudates The patients were discharged with no evidence of active ocular inflammation Within a week one patient returned with a violent exacerbation around the original lesion and in six weeks the second patient returned in the same condition Fortunately in both instances the disease was again controlled by prolonged streptomycin and adjuvant therapy It seems proba-

ble that in both these cases the violent recurrences were rebound phenomena here somewhat delayed by the streptomycin and adjuvant therapy Based on experimental analogy it is reasonable to assume that inhibition of phagocytosis and fibrosis by cortisone may have been related to these prompt recurrences

Whether the inhibition of inflammation phagocytosis and fibrosis by hormonal therapy operates adversely in other forms of granulomatous uveitis —those due to Brucella fungi treponema viruses—remains an open question to be answered in future investigations In the meantime the moral of present clinical and experimental observations seems clear When tissues are actually infected with pathogenic organisms the inflammatory reaction to infection is primarily a defensive mechanism It should not be interfered with or inhibited unless there is reason to believe that the infection will be overcome by the natural factors of resistance by specific chemotherapeutic or antibiotic measures or unless there is a secondary hypersensitivity reaction which in itself threatens destruction of vision In such cases cortisone or corticotropin may be given to control the subjective symptomatology of the disease and the secondary allergic inflammation around the lesions However, if no promise of natural or induced recovery can be detected and the secondary allergic reaction is not unduly threatening the natural pattern of the disease had best not be disturbed by hormonal therapy This is certainly true in tuberculosis probably true in syphilis and possibly true in other chronic infections of the eye In such granulomatous infections cortisone or corticotropin should not be used at all or if employed to control an alarming secondary allergic reaction their use should be guarded—never prolonged—and recognized as a calculated risk

As the early enthusiasm over hormonal therapy in ocular disease has subsided and more information has been obtained there is gradually emerging a realization of the actual therapeutic application of these hormones their limitations and contraindications to their use Much of their effect in certain specific conditions is still to be determined but the broad principles of their therapeutic action are becoming clear They are not curative agents their action is limited to control of the exudative and inflammatory phases of disease and even here their therapeutic range is limited The salient question to be considered before the hormones are used is simple Is the control of inflammation desirable? In many cases notably when the inflammation is the result of allergic toxic or physical insult the answer is an unequivocal Yes, in others such as ocular tuberculosis it is usually an equally positive No In a large group of chronic infections the answer is still undetermined In this last group the hormones will usually give early symptomatic relief but against this favorable action must be weighed the attendant disadvantages inhibition of fibrosis of phagocytosis and of neovascularization If specific therapeutic procedures are available to compensate for the loss of these reparative phenomena then the symptomatic relief afforded by the hormones is a blessing for both patient and ophthalmologist On the other hand if adequate specific therapeutic procedures are not available and

an alarming secondary allergic reaction has not occurred it would appear that hormonal therapy should be used most guardedly in chronic ocular infections

Summary

1 Cortisone and corticotropin have a definite but limited role in ophthalmic therapeutics Their favorable action is limited to control of inflammation and exudation They have no antibiotic or chemotherapeutic action and act not on the cause of disease but on the reaction of the tissues to a cause or irritant

2 When ocular inflammation is the result of acute trauma (allergic, toxic or physical) the reaction of the tissues is usually self limited and the control of inflammation with hormonal therapy during the natural course of the tissue reaction may simulate a complete cure Cortisone and corticotropin therefore find their highest usefulness in allergic reactions of the external eye and nongranulomatous inflammations of the uveal tract

3 In chronic granulomatous uveitis the effect of the hormones is not so spectacular Recurrences after cessation of treatment are frequent

4 When employed to suppress the inflammatory reaction due to chronic infection of the tissues, hormonal therapy should always be accompanied by specific antibiotic or chemotherapeutic procedure to eliminate the basic underlying infection

5 The hormones have no effect in the usual degenerative diseases of the eye There is a possibility however that they may be effective in ocular disease related to fibrinoid degeneration

6 Use of cortisone and probably of corticotropin is usually contraindicated in any form of ocular tuberculosis and should be guarded in chronic granulomatous infections Their chief value in chronic granulomatous disease is limited to control of the secondary allergic reaction

7 In disease of the external eye and anterior ocular segment the preferable method of treatment is the topical use of cortisone as either an ointment or a collyrium

8 In disease of the posterior ocular segment the parenteral administration of cortisone or corticotropin is preferable In severe, resistant cases the intravenous use of corticotropin may be indicated

9 Experimental studies in which various ocular reactions were used as indexes, have shown that cortisone and hydrocortisone topically or parenterally administered and corticotropin parenterally administered, (a) suppress the various recognized ocular hypersensitivity reactions, ocular reactions due to irritants and inflammation due to infection (b) inhibit neovascularization of the cornea (c) reduce fibroblastic activity in the stroma of the cornea and regeneration of the corneal endothelium (d) radically alter the pathogenesis of ocular tuberculosis changing the picture in the immune-allergic rabbit from a restrained fibrotic process into a necrotizing caseating destructive lesion and (e) influence the granulomatous lesions produced by Brucella organisms Further, the adrenocortical hormones, either secreted or administered, may be concerned in the pathogenesis of diabetic retinopathy

10 The mechanism of the therapeutic action of cortisone and corticotropin in ocular diseases is as yet undetermined but present indications are that it results from a direct action of the adrenocortical hormone at the local cell level

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12

Gastrointestinal Diseases

Thomas E Machella

Very little has been published in connection with the effects of cortisone upon the human stomach That cortisone may influence gastric function is suggested by isolated case reports in which peptic ulcer or its complications were recognized for the first time during treatment with cortisone or corticotropin Another indication is the reported action of corticotropin in stimulating gastric secretion In this chapter an attempt is made to summarize *reported experiences dealing with the effects of cortisone upon gastric secre-*tion and the clinical course of peptic ulcer Also discussed are reports of patients in whom peptic ulcer manifestations were first recognized during hormonal therapy of other diseases as well as pertinent observations in experimental animals Under appropriate headings the effects of cortisone upon liver function hepatic coma and the clinical course of hepatic diseases will also be evaluated as will its action in peritonitis and such disorders as sprue celiac disease regional enteritis and ulcerative colitis

Effect of Cortisone upon Gastric Secretion

Gastric Acidity The effects of cortisone upon gastric acid secretion in man have not been studied extensively More work on this important problem is required especially in patients receiving the compound for prolonged periods Gray et al [1] observed no significant changes in gastric acid or pepsin secretion during the 24 hours following oral administration of 500 mg of cortisone to 4 patients with active peptic ulcer Sandweiss et al after administering a total of 1 3 Gm of cortisone over a period of 11 days found that the nocturnal secretion of free hydrochloric acid was greater in 2 cases of duodenal ulcer than before cortisone was prescribed *A parallel to these* findings is contained in the study of Gray et al [1] with corticotropin in which daily doses of 80 to 120 units over a period of 10 to 21 days produced an increase in the gastric acidity found on serial aspirations in 7 fasting patients

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(3 with "normal" stomach 1 with healed gastric ulcer 1 with healed duodenal ulcer) and in the 12 hour nocturnal secretion of 3 patients one of whom had a healed duodenal ulcer They also observed a significant rise in gastric pep in concentration within 7 to 14 days Their investigation was not controlled by the administration of placebos

The influence of cortisone upon the gastric acid secretion has been studied somewhat more extensively in experimental animals than in human beings Davenport and Chavré[3] observed no effect upon the secretion of free hydrochloric acid following the injection of cortisone into normal mice and no difference in the rates of gastric secretion of adrenalectomized mice and the controls These as well as other observations led them to conclude that the hormones of the adrenal cortex do not play a direct or important role in the mechanism by which acid is secreted Madden and Ramsburg[4] studied the effect of cortisone administered to rats at varying times after pyloric ligation followed by adrenalectomy upon the volume and pH of gastric juice The e authors observed that adrenalectomy decreased the gastric secretion and that cortisone was effective in partially preventing this effect when administered one hour (but not 16 hours) before the procedure was undertaken They speculated concerning the possible influence of the adrenals on gastric secretion which might act through alterations in water and electrolyte balance Friedman Sandweiss and Saltzstein[5] found that both fasting and stimulated secretions were consistently higher in Mann Williamson dogs treated with cortisone than in the untreated animals The values however were within the limits obtained in normal dogs but they felt this may have been caused by the fact that the treated animals were in better general physical condition than were the untreated animals

Uropepsin Excretion A rise in uropepsin excretion occurring in most instances within 24 to 72 hours after oral or parenteral administration of 250 mg of cortisone daily was observed in normal subjects by Gray et al [6] The average increase was 88 per cent which was not as great as that observed by the authors following administration of corticotropin [1]

Cortisone and Peptic Ulcer

The influence of cortisone on the clinical course of peptic ulcer has been variously described Sandweiss et al [2] administered 1 3 Gm of cortisone over a period of 11 days to 2 patients with active duodenal ulcer Definite improvement occurred in 1 and no change was observed in the other In the latter instance laparotomy disclosed that the ulcer had penetrated into the pancreas Bauer[7] included 3 or 4 patients with known duodenal ulcer in his group of arthritic patients who were given adrenocortical therapy 1 of these had bled about four weeks prior to hormonal therapy In none were complications such as perforation or hemorrhage encountered during administration of cortisone or corticotropin Hench[8] observed that the peptic ulcer of 3 or 4' patients with rheumatoid arthritis was not activated or aggravated by cortisone even though the compound was sometimes administered for prolonged periods

On the other hand, Kirsner, Klotz and Palmer[9] believed that administration of a total of 800 mg of cortisone over a period of 10 days reactivated a gastric ulcer in one of their patients in whom symptoms appeared within five days after the institution of cortisone therapy This patient had experienced similar symptoms three months previously before cortisone was administered *Hench[8] observed that the duodenal ulcer of one of his rheumatoid* arthritis patients became aggravated each time cortisone was given orally In a group of 60 rheumatoid arthritis patients receiving prolonged cortisone or corticotropin therapy Ragan[10] had 3 cases of known duodenal ulcer which was present before either of the hormones was administered In 2 of these 3 surgical procedure was performed because of hemorrhage

Case histories of at least 4 patients in whom manifestations of peptic ulcer were ascribed to cortisone therapy have been reported in detail [11–14] In none of them however was there absolute proof of the absence of ulcer prior to therapy These case histories include the appearance of lesser curvature gastric ulcer three months after the administration of a total of 9 Gm of cortisone [11] perforation of an anterior duodenal ulcer on the fifteenth day of cortisone therapy when a total of 3 Gm had been given [1] a fatal hemorrhage from an acute gastroduodenal ulcer which occurred six days after completion of a two week course of cortisone in which a total of 1 7 Gm was administered [13] and hemorrhage from either a gastric or duodenal ulcer five and one half months after institution of treatment during which a total of 8 55 Gm was given [14] In addition to these cases Young and Rodstein[1] reported probable activation of a duodenal ulcer in one of their patients treated with cortisone for rheumatic fever a gastric hemorrhage occurred after 21 days of treatment and roentgenographic evidence of the ulcer persisted for five months thereafter On the other hand an unusual tendency toward the development of peptic ulcer has not been uniformly noted in patients receiving cortisone therapy Bauer[7] did not observe the appearance of ulcer symptoms in patients treated with either cortisone or corticotropin and Rose[16] observed but one ulcer in a group of 200 patients on long term hormonal therapy for allergic disorders primarily asthma

Although there is a certain amount of circumstantial evidence and a widespread belief that cortisone administration may predispose a *patient to* the development of peptic ulcer it would appear that the case has not as yet been satisfactorily established In the first place the opinions of clinicians with vast experience are not in agreement Secondly peptic ulcer is a natural occurrence in rheumatoid arthritis as shown by Bauer s survey [7] which revealed an incidence of 4 5 per cent of peptic ulcer in 650 cases The incidence was somewhat higher in males (6 5 per cent) than in females (3 per cent) In Ragan s experience [10] about 6 to 8 per cent of rheumatoid arthritis patients have a history of peptic ulcer It would be helpful to have a properly controlled survey of the incidence of peptic ulcer in large groups of patients receiving cortisone for prolonged periods of time Gastric analyses and roentgenographic examinations of the stomach and duodenum should be made before cortisone is instituted It is well known that peptic ulcer may exist

without the appearance of symptoms until some complic hemorrhage or perforation first makes its presence known. Th ult obtained in animal studies do not support the theory th sone tends to favor the development of peptic ulcer in fact Sandwei s et al[2] indicates that cortisone may exert a favora The e authors administered a total daily dosage of 20 mg of tate subcutaneously or intramuscularly to 6 dogs prepared acc Mann Williamson technic The hormone was first given 13 to the operation and continued throughout the life of the animal postoperative survival time of the cortisone treated animals w of the 11 control animals and about 40 per cent longer than t when corticotropin was given to animal on which the same o been performed Only 1 of the 11 control animals survived s contrast to 4 of the 6 cortisone-treated animals The animals w cortisone were observed to be in better general physical condi controls and had fewer postoperative visceral adhesions

Sprue

Favorable results have been reported to follow the admi cortisone to patients with sprue Similar observations have b the author In addition a possible rationale for the use of cor disease was supplied recently by Diéz Rivas Hernández Moral pi ch[17] who found laboratory and clinical evidence of decrease tical activity in approximately 40 per cent of patients with tr

Adlersberg Colcher and Drachman[18] treated 4 cases of non 1 of tropical sprue with cortisone in amounts varying from 0 over a period of 5 to 77 days The patients received eight cou ment in five of which the compound was administered intramu in three orally The initial dosage was 100 mg per day given divided doses Clinical and symptomatic improvement was obse of the 5 patients during therapy The extent of improvement de the length of treatment and varied in each individual In gen tients felt stronger became more alert developed increased app fewer stools and during prolonged courses of therapy gained torrhea persisted but the amount of fecal fat decreased Th tolerance curve improved in 1 case but was unaltered in the oth relapses occurred one to five weeks after cessation of therapy

Pollack[19] observed a clinical remission in a patient with nontr who received 100 mg of cortisone daily by the intramuscular ro tion of the dose to 25 mg twice a week resulted in a return o which subsided once more when the dosage was increased S maintained in clinical remission on a regimen of 50 mg orally e

response, in his opinion was not striking but each patient showed some improvement either subjectively or in a lessening of diarrhea

Taylor et al [1] treated 6 cases of nontropical sprue, 5 by the oral and 1 by the intramuscular route The amount of cortisone given varied from 25 to 100 mg daily These patients experienced an increase in appetite and in strength disappearance of abdominal cramps and distention and a decrease in number and volume of stools The fecal loss of water decreased and nocturnal diuresis lessened Edema of the extremities increased when amounts in excess of 75 mg were administered Blood pressure became elevated in 1 patient but returned to its usual level when the dose was decreased The condition of these patients reverted to pretreatment status following discontinuation of the hormone Data on the metabolic balance were obtained in 2 patients During the period of clinical improvement there occurred *an improved absorption of vitamins A and K a decreased loss of fat* and nitrogen in the feces and a diminished fecal solid and water content The serum albumin increased while the globulin tended to be lowered Sodium and chloride balances were generally positive but became negative after cortisone was discontinued The potassium tended to be inversely related to the sodium and chloride balance Calcium and phosphorus balances were inconsistent The authors ascribed the improvement chiefly to more efficient intestinal absorption but thought that better utilization of diet also played a part They stated that it appeared that cortisone offered the most effective means of treating nontropical sprue in exacerbation though its importance in the long term management of the disease remained to be evaluated

Celiac Disease

Ugland Wennevold and Salomonsen [2] treated a case of celiac disease with 940 mg of cortisone over a period of seven weeks and another with cortisone *(462 mg) and corticotropin (156 units) for six weeks* They observed improvement in the general condition mood appetite appearance and fat content of stools degree of iron deficiency anemia hypoproteinemia and glucose tolerance test No effect was noted upon the osteoporosis retarded development of the epiphyseal nuclei or roentgenographically demonstrable changes in the small intestine Two other cases treated only with corticotropin also responded favorably

Regional Enteritis

The occurrence of arthritis and erythema nodosum in some cases of regional enteritis led to a trial of cortisone in this disease Machella and Hollan [3] administered 1 5 Gm of cortisone subcutaneously *for a period of 10* days to 3 patients severely ill with regional enteritis Institution of therapy was followed by a sense of well being improved appetite disappearance of arthritic phenomena subsidence of fever and diarrhea change in character of stools from liquid to formed gain in weight decrease in erythrocyte sedimentation rate (E S R), and increase in hemoglobin The total number of

circulating eosinophils fell following the administration of cortisone No change in the roentgenographic appearance of the diseased portion of the bowel was detectable at the end of the period of therapy Transient or prolonged relapse occurred in each case after cessation of therapy Since then 12 additional patients with attacks of arthritis and erythema nodosum have been treated and prompt improvement occurred in all but 1 [34] In regional enteritis in the author's experience cortisone has been as effective orally as

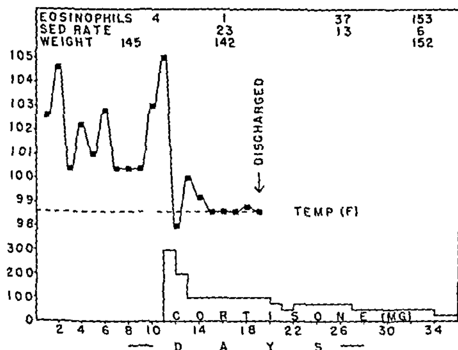


FIG 44 This chart illustrates the prompt and dramatic response to cortisone of a 20 year-old male with regional enteritis The episode treated was a relapse which occurred one year after the proximal colon and about one half of the ileum had been removed surgically It will be noted that promptly on institution of oral cortisone therapy fever (F) subsided In addition appetite returned and a sense of well being developed Subsequently the E S R (mm per hour) decreased and the patient gained weight He is still in remission seven months after termination of therapy

when injected Some of the patients have been maintained for periods extending to 10 months on daily maintenance doses varying from 25 mg for children to 50 and 75 mg for adults

The administration of cortisone has induced dramatic remissions in several instances (Figure 44) despite a previously walled off perforation of the bowel active bleeding and massive edema as a result of hypoproteinemia The results reported by other authors have been somewhat less satisfactory on the whole but in certain instances favorable effects have been observed Redish [5] administered 50 mg of cortisone twice daily for 10 days to 2 patients with regional enteritis In 1 he observed that the disappearance of

arthritic phenomena was accompanied by subjective improvement, a decrease in number of daily stools from 5–8 to 3–5 and roentgenographic evidence of improvement in small bowel function. An area of organic narrowing was not influenced. Symptoms recurred following discontinuation of therapy. In the second case the administration of cortisone was attended by the disappearance of arthritic phenomena, but diarrhea and abdominal cramps persisted.

Improvement in regional enteritis following the use of corticotropin has also been observed. The reported instances include 4 cases treated by Astwood et al.,[8] 2 by Gray et al.,[8] 3 of the 4 cases treated by Kirsner, Palmer, and Klotz,[28] and the experience of Stanley, Rosenberg, and Cleroux,[9] who obtained excellent response in 7 cases and moderate in 1 case which was complicated by coexisting psychoneurosis. In the majority of instances relapses occurred at varying intervals after cessation of the hormonal therapy. Kirsner, Palmer, and Klotz[8] felt that the response of regional enteritis to corticotropin was not as satisfactory as that observed in ulcerative colitis.

Ulcerative Colitis

Results of the treatment of ulcerative colitis with cortisone have not been as favorable as those obtained with corticotropin. A summary of the cases treated with cortisone and reported in detail is contained in Table 29. The good results reported in 46 per cent of 26 cases are in contrast to the effect of

Table 29

SUMMARY OF RESULTS OF CORTISONE THERAPY IN ULCERATIVE COLITIS

Author	*Number of Patients Treated*	*Favorable Response*	*Total Amount Administered (Gm.)*	*Duration of Administration (Days)*
Machella and Hollan[3]	3	2	1.5	10
Redish	5	0	1 to 2	10 to 12
Dearing and Brown[3]	4	2	5 to 4.4	5 to 44
Cailland and Demole[3]	1	1	4*	30
Kirsner and Palmer[3]	5	1	1.9 to 4.525	10 to 20
McKell, Tuthill, and Sullivan[33]	1	1	1.[illegible]	12
Milanes et al.[3]	2	2	2.[illegible]5 to 3	15 to 20
Gray et al.[35]	5	3	2.5 to 8.05	10 to 48
Total number of cases	26	12		

* Also received desoxycorticosterone

corticotropin in 117 collected cases 67.5 per cent of which showed remission[14] The apparent greater effectiveness may be caused in part by the fact that fewer cases have been treated with cortisone and that the hormone was administered in insufficient amounts in some instances Kirsner and Palmer[22] were more impressed with the action of corticotropin than with that of cortisone In 3 of their patients corticotropin was believed to be vastly superior to cortisone in inducing remission and 1 patient after failing to respond to cortisone administered orally or by injection obtained dramatic improvement with corticotropin They felt however that larger quantities of cortisone might prove more effective Fulin Kern and Almy[27] reported a localized perforation of the colon in 1 and acute perforation with generalized peritonitis in 2 of 17 patients treated with corticotropin Since these complications take place in patients with ulcerative colitis who are not receiving adrenocortical therapy the role of such therapy in their production is uncertain

When remission occurred during the administration of cortisone it usually was prompt and characterized by an increased sense of well being cessation of fever development of excellent appetite and gradual subsidence of diarrhea Erythema nodosum and arthritic manifestations when present promptly disappeared Roentgenographic and sigmoidoscopic evidences of improvement were not always observed during the period of clinical improvement

Gray[17] has reported the results of long term therapy with oral cortisone in ulcerative colitis Nine patients were treated for periods ranging from 3 to 17 months and a favorable response was produced in all of these excellent results being obtained in 6 patients and fair results in 3

Not all cases of ulcerative colitis have responded to cortisone In the author's experience the patients most benefited were those who were greatly debilitated or had an initially low total circulating eosinophil count and those with associated small intestine involvement Patients not responding were those who were in good general condition or had normal to high eosinophil counts which did not fall during therapy with cortisone and those with seemingly hopeless emotional motivating mechanisms Cortisone like corticotropin does not cure ulcerative colitis any more than it cures arthritis or any of the other chronic diseases whose manifestations it relieves A relapse may occur following discontinuation of treatment if the emotional problems involved have not been satisfactorily resolved during the period of improvement When remission has been induced by hormonal treatment and the emotional problems remain unsolved prolongation of the remission may be obtained by administration of maintenance doses If relapse occurs while the patient is receiving maintenance therapy a prompt increase in the dose is indicated

Peritonitis

Boling et al[18] observed that both child and adult patients with peritonitis responded more rapidly to chemotherapy combined with cortisone

or corticotropin than to chemotherapy alone The peritonitis was secondary to a variety of causes including extravasation of bile and ruptured appendixes More rapid disappearance of toxicity and return of normal gastrointestinal function were noted in the extremely toxic patients so treated

Cortisone and the Liver

The effects of cortisone upon liver function tests of patients with and without primary hepatic disease have been studied In addition its influence on the clinical course of hepatitis with and without coma and of chronic hepatitis has been evaluated

Effect upon Liver Function in the Absence of Primary Hepatic Disease

Holmes and Percefull[39] observed little change in the liver function tests of 23 patients without primary hepatic disease when 100 to 300 mg of cortisone was given daily over periods of 14 to 96 days in a total dosage varying from 1 65 to 10 3 Gm The van den Bergh reaction serum bilirubin bromsulfalein dye excreting capacity prothrombin time total serum protein and albumin globulin ratio were essentially unaltered

Effect upon Liver Function and the Clinical Course of Hepatic Disease

Acute Hepatitis Butt et al [40] observed no significant changes in serum bilirubin or liver function tests in a patient with acute serum hepatitis superimposed upon a cirrhosis who received 50 mg of cortisone twice daily for a first period of 14 days and a second of 5 days Similarly they found no evidence of alteration in the physical findings or course of the disease in this patient On the other hand in a case of serum hepatitis observed by Rifkin et al [41] serum bilirubin decreased from 23 to 3 mg per 100 cc of blood alkaline phosphatase from 7 to 4 units cephalin flocculation from +3 to 0 and thymol turbidity from 70 to 5 units 11 days after completion of an 8 day course of cortisone therapy The patient was in a semistuporous condition when first given cortisone but within 24 hours after a parenteral injection of 100 mg the appetite returned and a sense of well being was experienced The same daily dose was continued for the next four days and then was reduced to 50 mg for another three days Improvement was maintained and the patient apparently made a complete recovery Havens Myerson, and Carroll[42] noted nothing unusual in the rate of recovery of 1 patient who received cortisone during the convalescent phase of viral hepatitis

Chronic Hepatitis The effects of cortisone upon the various liver function tests in patients with chronic hepatitis have been inconsistent and experiences have varied Hanger and Collins[43] administered 100 mg of cortisone to 3 patients in two equally divided daily doses for 15, 17, and 28 days respectively In each instance jaundice lessened and the serum globulin chiefly the euglobulin fraction decreased The cephalin flocculation alkaline

phosphatase and bromsulfalein dye excreting capacity showed inconsistent changes A slight but definite increase in the serum albumin and an increase in the esterified cholesterol fraction were noted A prompt decrease in the size of the liver and a lessening of the jaundice were also observed but these changes were accompanied by a distinct increase in the tendency to retain fluids which was more marked than that usually following administration of comparable doses of cortisone to patients with other conditions especially those on a restricted salt intake This was particularly true of the formation of ascitic fluid

Gyorgy and Bluemle[44] administered cortisone in amounts varying from 0 6 Gm in six days to 2 8 Gm given in three courses over a period of six months to 5 patients with chronic hepatitis including 2 cases of the biliary type They observed a decrease in serum bilirubin varying from 0 13 to 3 1 mg and an increased excretion of urobilinogen (50 to 500 per cent) in all patients Thymol turbidity and gamma globulin were reduced significantly in 4 instances Glucose tolerance tests revealed temporarily decreased tolerance in 4 of the 5 patients Treatment with cortisone effected amelioration of the clinical condition in 2 patients worsened it in 1 and produced no change in 2 The authors felt that in certain cases of chronic liver disease however cortisone might be of value as a means of improving appetite

Havens Myerson and Carroll[4] observed diminished retention of bromsulfalein in 1 patient marked reduction of thymol turbidity in another and but little alteration in the cephalin cholesterol flocculation test in 7 patients with chronic hepatitis who received intramuscular injections of 50 to 100 mg of cortisone daily for periods ranging from 8 to 165 days Varying degrees of increase in edema or ascites were noted in 5 of these patients and euphoria with increased appetite occurred in 4 Two were clinically improved Edema and ascites increased rapidly in 2 others who became stuporous during or shortly after cessation of therapy one of these patients died In another patient fever associated with an infection of the urinary tract disappeared when cortisone was given and reappeared when it was discontinued Glycosuria occurred in this patient during the latter part of therapy and continued for 10 days after cessation of cortisone A glucose tolerance test at this time revealed results that were diabetic in type

Holmes and Lerecfull[39] found no evidence that the liver function was impaired in any way by the daily administration of cortisone in total amounts of 2 1 and 2 3 Gm for 14 and 18 days respectively to 2 patients with chronic hepatitis No significant alteration occurred in the course of the disease although improved appetite and moderate improvement in the sense of well being were noted Butt et al [40] found no change in the serum bilirubin liver function tests or the lipemia in 1 patient with biliary cirrhosis and severe hyperlipemia who received 100 mg of cortisone intramuscularly twice daily for a period of 12 days The physical findings and the course of the disease were similarly unaffected Blahd et al [45] found that the administration of desoxycorticosterone cortisone and corticotropin at separate periods accelerated the development of ascites and edema in patients

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Gyorgy and Bluemle[44] administered cortisone in amounts varying from 0.6 Gm. in six days to 2.8 Gm. given in three courses over a period of six months to 5 patients with chronic hepatitis, including 2 cases of the biliary type. They observed a decrease in serum bilirubin varying from 0.13 to 3.1 mg. and an increased excretion of urobilinogen (50 to 500 per cent) in all patients. Thymol turbidity and gamma globulin were reduced significantly in 4 instances. Glucose tolerance tests revealed temporarily decreased tolerance in 4 of the 5 patients. Treatment with cortisone effected amelioration of the clinical condition in 2 patients, worsened it in 1, and produced no change in 2. The authors felt that in certain cases of chronic liver disease, however, cortisone might be of value as a means of improving appetite.

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Holmes and Percefull[39] found no evidence that the liver function was impaired in any way by the daily administration of cortisone in total amounts of 2.1 and 2.3 Gm. for 14 and 18 days, respectively, to 2 patients with chronic hepatitis. No significant alteration occurred in the course of the disease, although improved appetite and moderate improvement in the sense of well being were noted. Butt et al.[40] found no change in the serum bilirubin, liver function tests, or the lipemia in 1 patient with biliary cirrhosis and severe hyperlipemia who received 100 mg. of cortisone intramuscularly twice daily for a period of 12 days. The physical findings and the course of the disease were similarly unaffected. Blahd et al.[45] found that the administration of desoxycorticosterone, cortisone and corticotropin at separate periods accelerated the development of ascites and edema in patients

with hepatic cirrhosis A marked withdrawal diuresis of sodium and water followed discontinuance of these agents, in some instances this was sufficiently pronounced to remove all edema and ascites

Hepatic Coma In 2 cases of hepatic coma on the basis of a fulminant hepatitis Ducci and Katz[46] reported recovery following the administration of cortisone One patient recovered from the coma eight hours after an intramuscular injection of 500 mg of cortisone the other, treated with cortisone corticotropin Terramycin and aureomycin became conscious on the fourth day of treatment Depressed alpha and beta globulins returned to normal in both cases A third patient died in coma one hour after receiving the first dose of cortisone Three other patients with more chronic forms of hepatitis also died One was treated with cortisone and corticotropin a second with cortisone and Terramycin and a third with cortisone Terramycin, and aureomycin

Effect upon the Microscopic Appearance of the Liver

Hanger and Collins[43] noted a decrease in the cellular infiltration of the diseased portions of the liver in 2 cases of chronic nonalcoholic hepatitis treated with cortisone but active necrosis of parenchymal cells was not abolished Steinberg Webb and Rafsky[47] administered 5 075 Gm of cortisone intramuscularly to a patient with acute rheumatic fever for a period of 43 days The liver became palpable on the sixth day of therapy after a total dose of 1 5 Gm Signs of congestive heart failure were not present A punch biopsy of the liver revealed the hepatomegaly to be caused by fatty infiltration Seven days after discontinuance of cortisone the liver became smaller A biopsy performed 14 days later revealed normal liver tissue In 1 case of portal cirrhosis[39] biopsy performed after cessation of cortisone therapy revealed no essential difference in the appearance of the liver from that found prior to therapy

Summary

1 The reported effects of cortisone upon gastric secretory function and the clinical course of peptic ulcer may be summarized as follows

Single doses of cortisone have not influenced gastric acidity or pepsin secretion in patients with active peptic ulcer nor have they affected gastric secretion in normal or adrenalectomized mice

Repeated doses of cortisone over prolonged periods of time have been observed to give rise to (1) a higher nocturnal secretion of free hydrochloric acid in 2 cases of duodenal ulcer (2) an increase in uropepsin excretion in normal subjects and (3) in Mann Williamson dogs an almost normal gastric acidity in the cortisone-treated group in contrast to the reduced acidity found in the controls

The influence of repeated cortisone administration on the clinical course of known peptic ulcer has been variously described as beneficial aggravating or without effect

The first recognition of the symptoms or complications of ulcer during cortisone therapy has been recorded in at least 4 cases. In three the manifestations or complications appeared after cortisone had been administered for one-half to five and one-half months. In a fourth case hemorrhage from a gastroduodenal ulcer occurred six days after a two-week course of cortisone had been completed, the hemorrhage having occurred after the patient was discharged from the hospital. Hemorrhage from a duodenal ulcer in a fifth case was attributed to "probable activation" of a duodenal ulcer as a result of cortisone.

Some authors with vast experience have not observed an unusual tendency toward the development of ulcer manifestations in patients receiving cortisone for prolonged periods of time.

The possibility of development of peptic ulcer or of its more serious complications should always be kept in mind while cortisone is being administered. Additional data based upon carefully controlled studies, however, are required to settle some of the points which have been raised.

2. The results of cortisone therapy in patients with sprue and celiac disease have been in general satisfactory. Whether administered orally or by injection, the compound has been effective in producing and maintaining remission. Relapses have occurred following discontinuance of cortisone. Continued administration is usually required to maintain remission.

3. The results of cortisone therapy in regional enteritis and ulcerative colitis have been variable. In some instances definite and dramatic improvement has been ascribed to the compound; in others a favorable response has not been obtained. Continued therapy has been required in some cases to maintain remission.

4. The disappearance of toxicity and the return of gastrointestinal function to normal in patients with peritonitis have been observed to be more rapid following combined cortisone and chemotherapy than after chemotherapy alone.

5. The administration of cortisone to patients with acute or chronic hepatic disease has been associated with variable results. Too few cases of acute hepatitis have been treated to permit any conclusions. The course of the disease varies so much from patient to patient that proper evaluation requires large series properly controlled.

Experience with chronic hepatitis in general indicates that cortisone may increase appetite and give rise to a sense of well being. Certain undesirable effects, such as increased ascites and edema, and even coma and death, have attended its use. Reduction in amount of fat, fibrosis, and inflammatory cells in the liver has been reported in certain patients, while in others biopsy revealed no demonstrable changes. Alterations in the commonly employed liver function tests have been either slight or insignificant. Slight reduction in total serum bilirubin concentration and bromsulfalein retention as well as increased urobilinogen excretion has been described by some, but others have found no significant variations.

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other controlling mechanisms which oppose the action of the 11 oxysteroids There is probably more distinction than difference between these alternative explanations but the possible therapeutic effects of cortisone and corticotropin can best be understood in terms of their modifying influence on the processes which selectively control the growth and differentiation of the various types of blood cells as well as on pathologic tissue reactions which lead to the elaboration of lytic or otherwise injurious substances

Applications of Adrenocortical Therapy in Diseases of the Blood

The effects of administration of cortisone or corticotropin have been noted in patients suffering with a wide variety of hematologic conditions including those associated with specific deficiencies inherited abnormalities infections and intoxications It is however in three broad categories of disease affecting the blood and blood forming organs that these agents have proved especially effective in modifying the course of the illness in some instances they have provided the only definitive therapy available These categories are (1) hypersplenism manifested by pancytopenia or by selective cytopenias (2) disseminated neoplasms of the hemic and lymphatic systems and (3) myeloid hypoplasias of either known or obscure etiology

Objectives of Therapy Depending upon the natural history of the disease and the particular hazards and special problems which may arise during its course the objectives of treatment with cortisone or corticotropin will differ in the groups of conditions listed above in their various subdivisions and in each individual case

Certain of the hypersplenic disorders notably idiopathic thrombocytopenic purpura of short duration and sometimes acute acquired hemolytic anemia are characterized by a tendency to undergo spontaneous remission In such instances one must assume that hemic homeostasis has been restored either by the subsidence of a self limited process such as an acute infection or by a successful effort on the part of the body to overcome the factors producing imbalance and so reestablish normal equilibrium between cell production and destruction In some cases the administration of cortisone or corticotropin promptly initiates lasting remission comparable to that which may occur spontaneously but with a pattern of response and frequency of occurrence which clearly indicate that they are hormone induced However, even in those cases of hypersplenism which are only transiently benefited by hormonal therapy temporary arrest of the process may serve to control a serious hemorrhagic episode in a patient with idiopathic thrombocytopenic purpura to overcome a resistant infection in one with splenic neutropenia or to prepare adequately a patient with acute acquired hemolytic anemia for splenectomy

In acute leukemia the goal of steroid therapy is reestablishment for a time of nearly normal functional hemopoiesis whereas in chronic cases of leukemia and lymphoma in advanced stages cortisone may be useful in partially suppressing neoplastic cell growth and in producing temporary palliation

13

Blood Diseases and Malignancy

Frank H Bethell

Influence of the Adrenal Cortex and of 11-Oxysteroids on the Hemic Equilibrium

The part played by the adrenal cortex in the maintenance of blood cell levels is not well understood Mechanisms concerned with cell proliferation development and release from tissues of origin as well as those having to do with removal and destruction of circulating corpuscular elements are undoubtedly influenced by a number of factors which together constitute a system of forces the function of which is to maintain a steady state in health and at the same time provide for controlled and limited responses to stimuli arising from environmental situations Although characteristic alteration in blood values are found in association with gross dysfunction of the adrenal cortex such as the anemia of Addison s disease[1] and the polycythemia commonly observed in Cushing s syndrome the changes are usually slight or moderate and as a rule constitute only a minor part of the disease picture

A decrease in circulating lymphocytes due apparently, both to lysis of developing cells in lymph tissue[3] and to suppression of growth of lymphocytes [4] follows the injection of cortisone hydrocortisone or corticotropin Eosinopenia and neutrophil leukocytosis together with evidences of increased erythrocytic proliferations are associated with stimulation of the adrenal cortex[5–7] or with the administration of 11 oxysteroids However these changes are not progressive with continued administration of the hormone and the leukocyte values except for eosinopenia tend to revert toward normal in spite of other evidences of persistent metabolic effect It must, therefore be presumed that cortisone and corticotropin either have a limited influence on hemopoiesis or that hemic equilibrium is restored by

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From The Thomas Henry Simpson Memorial Institute for Medical Research and the Department of Medicine University of Michigan Medical School Ann Arbor Michigan

ment in the vascular component of the hemorrhagic diathesis which preceded and appeared to be largely *independent of the effect upon the thrombocytes*.

The concept of two abnormalities operating independently in thrombocytopenic purpura has received support from the observations of Faloon Greene and Lozner [14] who administered either cortisone or corticotropin to 4 patients with idiopathic thrombocytopenic purpura and to 3 with purpura and thrombocytopenia associated with leukemia. In 2 of the former group complete remission occurred, with improvement in vascular resistance preceding rises in platelet counts. In all of the other patients vascular resistance increased without change in the platelet values. These authors conclude from such observations that cortisone or corticotropin may induce an improvement in vascular resistance which is not necessarily accompanied by increased platelet production. On the other hand as suggested by Evans and Liu [15] failure to demonstrate a rise in the platelet count does not necessarily indicate a lack of production since the elements may be leaving the circulation or adhering to vascular walls as rapidly as they are released into the blood stream. It is undoubtedly true that the integrity of the vascular walls may be impaired by a number of metabolic derangements such as nonthrombocytopenic hypersensitivity reactions which may be influenced by 11 oxysteroids but it remains to be proved that the abnormal vascular resistance in idiopathic thrombocytopenic purpura is caused wholly or in part by a mechanism other than lack of thrombocytes.

Most of the published reports on the use of cortisone and corticotropin in idiopathic thrombocytopenic purpura include only a few cases and because of the variability of the clinical course and manifestations of this disease compilation of data is apt to be misleading. Moreover some investigators apparently have failed to observe their patients for a sufficient length of time to determine the ultimate effect of hormonal therapy. The usual pattern of successful thrombocyte response to cortisone or corticotropin is an abrupt and progressive rise which develops within a few days of the start of treatment and often leads to platelet counts well above the normal range. On discontinuance of hormone administration a rather precipitous decline occurs although in favorable cases the count does not fall to pretreatment levels and purpura does not recur. Subsequently in those patients who have sustained remissions the thrombocytes increase spontaneously within a few days to a week and a gradual rise may continue for several months (Figure 4a).

The effect of cortisone or corticotropin in 3 patients with idiopathic thrombocytopenic purpura of the chronic form was reported by Jacobson and Sohier [16]. Two of these had previously had splenectomies followed by temporary remission. *In all 3 patients platelet counts rose to high levels* during hormone administration. In the 2 splenectomized patients relapses occurred when the dosage was reduced or the medication discontinued. The third patient underwent removal of the spleen while in a cortisone induced remission. The dosage of cortisone employed by these authors was 100 mg by mouth every eight hours and platelet levels within or above the normal

Patients with myeloid hypoplastic conditions may be benefited by cortisone or corticotropin administration, at least to the extent that fewer transfusions are required and it may occasionally be possible through the myeloid stimulatory action of these hormones to carry a patient through a phase of severe marrow intoxication or depression until reparative activity has time to become evident

Idiopathic Thrombocytopenic Purpura

Bleeding in idiopathic thrombocytopenic purpura is attributable to two defects, a vascular abnormality usually although somewhat inadequately described as capillary fragility and a lack of thrombocytes The clinical forms of the disease are so variable that a number of pathogenetic mechanisms have been postulated in its development [8] In general, three main types are recognized (1) acute usually self limited but sometimes unless treated, becoming fulminant with death in hemorrhagic crisis (2) chronic active, with unremitting clinical and hematologic changes (3) cyclic, characterized by periodic exacerbations and remissions In making these distinctions based on the natural history of the disease it must be acknowledged however, that chronic cases usually have a fairly definitely dated onset and that they represent instances of the condition which failed to remit spontaneously In the writer s experience approximately one half of a series of nearly 50 patients with thrombocytopenic purpura of short duration whose manifestations were not so severe as to require intervention failed to show evidence of spontaneous remission during at least a two months period of observation following the onset of purpura and for this reason most of them were subjected to splenectomy Unless a specific nonbacterial infection or drug reaction can be determined as a probable provocative factor in the development of thrombocytopenic purpura there is no known way of predicting which patients will undergo spontaneous remission nor can definite time limits be set for the occurrence of such remission Experience indicates however that few patients whose purpura lasts longer than four months will remit spontaneously This observation is of significance in the evaluation of cortisone and corticotropin therapy in idiopathic thrombocytopenic purpura since it is important in each case to bear in mind the probable course of the illness without treatment

The earliest reported observations of the effects of cortisone or corticotropin in idiopathic thrombocytopenic purpura were made by Robson and Duthie[9] and by Meyers Miller and Bethell [10] The former authors treated 2 patients with the disease with cortisone and observed decreases in capillary fragility before rises in thrombocyte values Although both patients were improved remissions were neither complete nor lasting after discontinuance of therapy Meyers and her associates initially reported that 3 of 5 patients with idiopathic thrombocytopenic purpura all of whom were treated with corticotropin obtained sustained complete remissions following therapy These authors in later publications[11–13] also called attention to the improve

ment in the vascular component of the hemorrhagic diathesis which preceded and appeared to be largely independent of the effect upon the thrombocytes

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The effect of cortisone or corticotropin in 3 patients with idiopathic thrombocytopenic purpura of the chronic form was reported by Jacobson and Sohier[16] Two of these had previously had splenectomies followed by temporary remission In all 3 patients platelet counts rose to high levels during hormone administration In the 2 splenectomized patients relapses occurred when the dosage was reduced or the medication discontinued The third patient underwent removal of the spleen while in a cortisone induced remission The dosage of cortisone employed by these authors was 100 mg by mouth every eight hours and platelet levels within or above the normal

range were attained in four days Corticotropin was given initially in daily doses of 50 or 100 units The prompt responses of these 3 patients with long standing thrombocytopenia are clearly attributable to the medication since the possibility of spontaneous remission can be excluded with reasonable certainty

Twelve patients with idiopathic thrombocytopenic purpura were given either cortisone or corticotropin by Wilson and Eisemann [17] Cortisone was given in a daily dosage of 50 to 100 mg the corticotropin was administered every day in a dose of either 40 units intramuscularly or 10 units intravenously in a continuous eight hour infusion Three patients had sustained

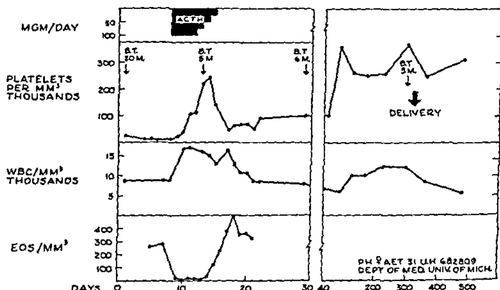


Fig 45 Sustained remission induced by corticotropin therapy in a 31 year-old woman with acute idiopathic thrombocytopenic purpura The patient completed pregnancy successfully Note the prompt rise of the platelets the fall on discontinuing therapy without recurrence of purpura and the subsequent slow recovery *Note* In this and related figures B T indicates bleeding time

remissions two following cortisone administration alone and one after both cortisone and corticotropin Two members of the series had transient responses and seven derived little benefit from hormonal therapy Of these 6 were splenectomized, 5 experiencing dramatic and lasting results up to the time of the report

Myers and her associates[18] reported thrombocytic responses to levels of normal or above in 12 of 17 patients with idiopathic thrombocytopenic purpura treated with cortisone or corticotropin Of these 5 had pending remissions of at least 16 months This series studied by the writer and his colleagues, has now been extended to include 23 cases of which all but 7 have had complete clinical and hematologic remissions In 9 of the patients remissions have been sustained A more detailed analysis of therapeutic results in this series will follow

In view of the reported experience of the authors cited it is somewhat surprising that Stefanini and his associates[18] were able to conclude that cortisone or corticotropin had no more than an equivocal or evanescent effect upon the number of circulating thrombocytes in some members of their series of 15 patients with acute or chronic idiopathic thrombocytopenic purpura and no effect upon the remainder. They obtained no sustained remissions but observed reduction in most cases of spontaneous bleeding manifestations and improvement in capillary fragility. The less favorable results obtained by these investigators may possibly be explained by inadequate dosage of the hormones. Cortisone was given in daily doses of 100 to 150 mg

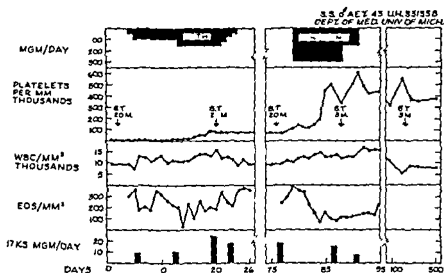


Fig 46 Slight response to corticotropin in a 43 year-old male with acute idiopathic thrombocytopenic purpura and complete sustained remission induced by cortisone (From Meyers Miller Linman and Bethell[13])

whereas the experience of the writer indicates that 300 mg daily is usually required to produce a prompt and maximal response

The widely divergent natural course and clinical manifestations of idiopathic thrombocytopenic purpura render each case almost an individual disease entity However certain generalizations based on a small but varied series may perhaps be allowed since they permit a preliminary evaluation of the application and usefulness of cortisone and corticotropin in this disease

An analysis of the results obtained in our series of 23 cases of idiopathic thrombocytopenic purpura treated with cortisone or corticotropin is presented in Tables 30 to 33 From these data the following conclusions of practical therapeutic significance may be drawn

1 Sustained remission induced by hormonal therapy may be expected in a limited number of patients with this disease (Figures 45 and 46) In our series the number so affected did not exceed the expected incidence of spon

range were attained in four days Corticotropin was given initially in daily doses of 50 or 100 units The prompt responses of these 3 patients with long standing thrombocytopenia are clearly attributable to the medication since the possibility of spontaneous remission can be excluded with reasonable certainty

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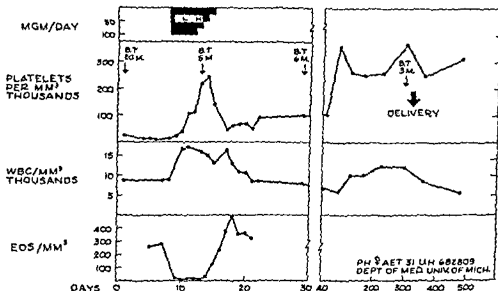


Fig 45 Sustained remission induced by corticotropin therapy in a 31 year old woman with acute idiopathic thrombocytopenic purpura The patient completed pregnancy successfully Note the prompt rise of the platelet the fall on discontinuing therapy without recurrence of purpura, and the subsequent slow recovery Note In this and related figures B T indicates bleeding time

remissions two following cortisone administration alone and one after both cortisone and corticotropin Two members of the series had transient responses and seven derived little benefit from hormonal therapy Of these 6 were splenectomized 5 experiencing dramatic and lasting results up to the time of the report

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Table 31

RESPONSE OF PLATELET COUNT IN RELATION TO CLINICAL EFFECTS, DOSAGE, AND DURATION OF HORMONAL THERAPY IN IDIOPATHIC THROMBOCYTOPENIC PURPURA

Platelet Count	*Clinical Effects*	*Duration of Therapy (days)*	*Hormone*	*Daily Dose*	*Number of Patients*
Restored to normal in 3-8 days	Complete remission	8 1	Cortisone	200-300 mg	9
			Corticotropin	100 units	9
Unaffected	Incomplete or no remission	11-23	Cortisone	300-400 mg	
			Corticotropin	100-160 units	4*

* Two of these patients failed to respond to corticotropin but subsequently obtained complete remission with cortisone.

derives little or no benefit from cortisone or corticotropin administration may still undergo complete remission following splenectomy (Figure 48).

2. The time required for thrombocyte increase to become apparent after institution of hormonal therapy is not more than a few days in those patients who have good, even though temporary, responses. If normal platelet levels are not attained within 10 days, it is exceedingly unlikely that prolonging therapy will have any further effect, unless the dosage has been insufficient. In our experience, an adequate therapeutic trial requires the

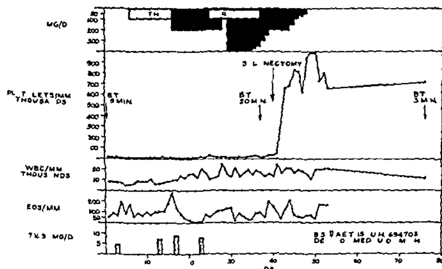


FIG. 48. Failure of both cortisone and corticotropin to induce remission in a 15-year-old girl with acute idiopathic thrombocytopenic purpura. Splenectomy was followed by an abrupt and sustained response. (From Meyers, Miller, Linman and Bethell.[12])

Table 30

CLINICAL RESPONSES TO CORTISONE OR CORTICOTROPIN IN TWENTY-THREE CASES OF IDIOPATHIC THROMBOCYTOPENIC PURPURA

Nature of Response	*Number of Patients*	*Subsequent Course*	*Number of Patients*
Complete	18	Sustained remission of 6–40 months	9
		Remission followed by relapse. Splenectomy was then performed in 8 patients with sustained remission. The ninth patient had undergone splenectomy previously	9
Incomplete	4	Splenectomy with remission	4
Slight	1	Splenectomy with remission	1

taneous remission, but the pattern of the responses and their time relationships to therapy clearly indicate that they were initiated by cortisone or corticotropin administration. Patients who relapse after a complete hormone-induced remission may be expected to respond again on resumption of medication. This characteristic of hormonal therapy is of importance since it permits reestablishment of control of the hemorrhagic tendency in patients who relapse after an initial therapeutic trial and who are considered candidates for splenectomy (Figure 47). The rare patient in our experience who

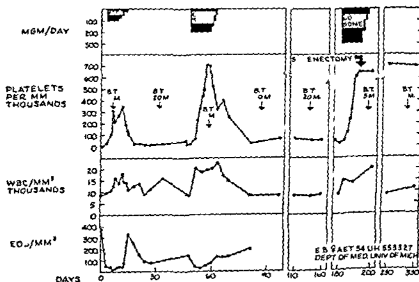


FIG. 47 Repeated remissions induced by cortisone and corticotropin followed by relapses in a 34-year-old woman who had had chronic recurrent thrombocytopenic purpura for eight years. Splenectomy was done while she was in cortisone-induced remission which has been sustained for two years. (From Meyer, Miller, Linman and Bethell.[13])

Table 31

RESPONSE OF PLATELET COUNT IN RELATION TO CLINICAL EFFECT: DOSAGE AND DURATION OF HORMONAL THERAPY IN IDIOPATHIC THROMBOCYTOPENIC PURPURA

Platelet Count	Clinical Effect	Duration of Therapy (Day)	Hormone	Daily Dose	Number of Patients
Restored to normal in 3-8 days	Complete remission	8-1	Cortisone	200-300 mg	1
			Corticotropin	100 units	9
Unaffected	Incomplete or no remission	11-23	Cortisone	300-400 mg	3
			Corticotropin	100-160 units	4*

* Two of these patients failed to respond to corticotropin but subsequently obtained complete remission with cortisone.

derives little or no benefit from cortisone or corticotropin administration may still undergo complete remission following splenectomy (Figure 48).

2. The time required for thrombocyte increase to become apparent after institution of hormonal therapy is not more than a few days in those patients who have good, even though temporary, responses. If normal platelet levels are not attained within 10 days, it is exceedingly unlikely that prolonging therapy will have any further effect unless the dosage has been insufficient. In our experience an adequate therapeutic trial requires the

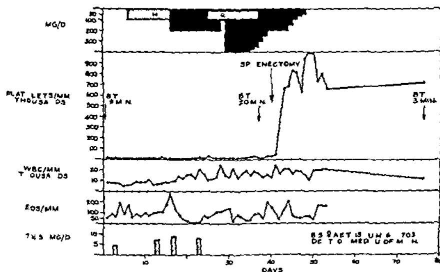


FIG. 48. Failure of both cortisone and corticotropin to induce remission in a 15-year-old girl with acute idiopathic thrombocytopenic purpura. Splenectomy was followed by an abrupt and sustained response. (From Meyers, Miller, Linman and Bethell.[13])

Table 32

LENGTH OF ILLNESS WITH REFERENCE TO TYPE AND DEGREE OF CLINICAL RESPONSE TO CORTISONE OR CORTICOTROPIN

Duration of Purpura (months)	*Total Number of Patients*	*Remissions*	
		Sustained	*Unsustained or Incomplete*
Less than 3	9	8	1
3–6	4	1	3
6–12	4	0	4
More than 12	6	0	6

Table 33

IMPROVEMENT IN CAPILLARY FRAGILITY DESPITE POOR THROMBOCYTE RESPONSE TO HORMONAL THERAPY IN FIVE CASES OF IDIOPATHIC THROMBOCYTOPENIC PURPURA

Patient	*Age*	*Sex*	*Platelet Count (thousands per cu mm)*		*Positive Pressure Capillary Fragility Test (Pumpel Leede)*	
			Before Therapy	*After Therapy*	*Before Therapy*	*After Therapy*
S B	9	F	9 400	22 000	+++	+
B S	15	F	5 000	30 100	++++	++
J B	49	F	5 000	25 800	++++	+
J W	58	M	5 000	17 100	+++	+
N S	59	F	36 000	95 000	+++	0

daily administration of 300 mg of cortisone usually given orally in fractional doses of 75 mg every six hours In the case of corticotropin the usual dosage is 100 units intramuscularly each day in doses of 25 units every six hours

3 Sustained remissions may be expected in most patients with idiopathic thrombocytopenic purpura who have had hemorrhagic symptoms for less than three months, whereas those whose history extends for longer than six months are almost certain to show incomplete responses or to relapse after discontinuing therapy

4 All patients with idiopathic thrombocytopenic purpura who are having active hemorrhagic manifestations may be expected to show improve

ment after cortisone administration even though no change in circulating thrombocytes occurs Such improvement is evidenced by a lessening of capillary fragility Exceptions to this statement probably will be observed but at present there appears to be no need to qualify it Beneficial effects from corticotropin therapy are, of course dependent upon the degree of adrenocortical response to stimulation

Acquired Hemolytic Anemia

It is in hemolytic anemias of the acquired type associated with autoimmunization that cortisone or corticotropin administration has produced especially spectacular results This disorder of obscure and probably multiple etiology is relatively uncommon but its incidence appears to be on the increase It may occur at any age but in our experience the idiopathic form is most frequently seen in middle life with a predominance in females of three to one The onset may be acute and the course rapidly progressive with fever and other evidences of toxicity or symptoms may develop insidiously without severe systemic manifestations In the former group there is often a history of preceding infection such as primary atypical pneumonia Some cases termed symptomatic or secondary as opposed to idiopathic are associated with disseminated malignancy especially malignant lymphoma and lymphocytic leukemia It is quite probable that this group of hemolytic anemias is due to hypersensitivity reaction and that it may be closely related to the collagen diseases In this respect the association of acquired hemolytic anemia and disseminated lupus erythematosus has been reported by Dubois[19] in 3 cases and a similar instance has been observed by the writer

The foregoing considerations emphasizing the immunologic nature of acquired hemolytic anemia and its relationship to connective tissue and lymphoreticular disorders provided a rational basis for the therapeutic trial of cortisone and corticotropin Early experiences with these agents in the treatment of acquired hemolytic anemia of autoimmune type were reported by Dameshek and by Gardner at the Third Annual Meeting of the Blood Club[20] Since then numerous reports have been published all dealing with relatively small numbers of cases but exhibiting remarkable agreement in their conclusions

Dameshek Rosenthal and Schwartz[1] observed almost complete remissions in 4 of 5 patients with acquired hemolytic anemia treated with corticotropin Two of the cases were of the idiopathic type and the remainder were associated with malignant lymphoma Coincident with the arrest of the hemolytic process there was disappearance of 'warm' hemagglutinin and marked diminution of cold agglutinin The Coombs test remained positive in all cases Relapse in the hemolytic process occurred soon after discontinuance of therapy in 2 patients and resumption of treatment resulted in second remissions In an addendum to this report the authors mention 3 additional cases of idiopathic acquired hemolytic anemia in all of which dramatic responses to corticotropin administration were obtained They state

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Duration of Purpura (months)	*Total Number of Patients*	*Remissions*	
		Sustained	*Unsustained or Incomplete*
Less than 3	9	8	1
3–6	4	1	3
6–12	4	0	4
More than 12	6	0	6

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IMPROVEMENT IN CAPILLARY FRAGILITY DESPITE POOR THROMBOCYTE RESPONSE TO HORMONAL THERAPY IN FIVE CASES OF IDIOPATHIC THROMBOCYTOPENIC PURPURA

Patient	*Age*	*Sex*	*Platelet Count (thousands per cu mm)*		*Positive Pressure Capillary Fragility Test (Rumpel Leede)*	
			Before Therapy	*After Therapy*	*Before Therapy*	*After Therapy*
S B	9	F	9 400	22 000	+++	+
B S	15	F	5 000	30 100	++++	++
J B	49	F	5 000	25 800	++++	+
J W	58	M	5 000	17 100	+++	+
N S	59	F	36 000	95 000	+++	0

daily administration of 300 mg of cortisone, usually given orally in fractional doses of 75 mg every six hours In the case of corticotropin the usual dosage is 100 units intramuscularly each day in doses of 25 units every six hours

3 Sustained remissions may be expected in most patients with idiopathic thrombocytopenic purpura who have had hemorrhagic symptoms for less than three months whereas those whose history extends for longer than six months are almost certain to show incomplete responses or to relapse after discontinuing therapy

4 All patients with idiopathic thrombocytopenic purpura who are having active hemorrhagic manifestations may be expected to show improve-

Meyers and her associates[13] reported observations in 7 patients with idiopathic acquired hemolytic anemia treated with cortisone or corticotropin. Of the seven patients, a 46-year-old woman with a probable duration of hemolytic anemia of at least two years underwent sustained clinical and hematologic remission which has now lasted nearly three years. Although this patient has no evidence of active hemolysis, incomplete antibodies in low titer continue to be demonstrable in her serum. Five other patients in the series experienced substantially complete remissions after either cortisone or corticotropin administration but relapsed when treatment was discontinued. Two of this group had severe thrombocytopenia associated with

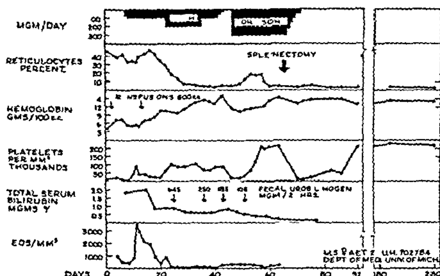


FIG. 49. Partial response to corticotropin in a 21-year-old woman with acute hemolytic anemia and thrombocytopenic purpura, who obtained complete although transient remission while receiving cortisone therapy. Splenectomy has resulted in sustained remission. (From Meyer, Miller, Linman and Bethell.[13])

their hemolytic anemia (Figures 49 and 50). Second responses were obtained prior to splenectomy in 4 of these patients. One of the 7 members of the series, a 65-year-old woman with an illness of three months' duration, failed to respond to corticotropin in a daily dose of 100 units and responded only partially to cortisone, 300 mg. daily. Splenectomy was done with but temporary improvement, and the patient has since been maintained for longer than two years on periodic courses of oral cortisone in doses of 50 or 75 mg. daily (Figure 51). It is of interest that whereas the titer of autoagglutinins generally falls as hemolysis decreases in response to steroid therapy, the opposite was true in this patient, who demonstrated a marked rise in the titer of autoimmune bodies at a time when partial clinical and hematologic remission was evident. The series reported by Meyers and associates[13] has now been extended to include 12 cases, and a summary of the therapy employed and the responses obtained will be presented later.

that cortisone in tablet form was found useful for continued *maintenance* therapy

One case of acquired hemolytic anemia associated with rheumatoid arthritis and a pneumonic inflammatory process and 2 cases of hereditary spherocytic anemia were treated with corticotropin by Davidson and his associates [2] The latter 2 were not benefited The patient with the acquired process underwent a dramatic remission with some evidence of recurrence after cessation of treatment but subsequently made a *complete recovery* It seems probable that this patient's hemolytic anemia was of the acute variety associated with primary atypical pneumonia Spontaneous recovery may be anticipated in such cases if the patient survives the acute process Because of the intense hemagglutination usually present transfusions are frequently of no value and may be detrimental and the outlook is often grave Cortisone or corticotropin administration may be lifesaving in such situations

Two children and one adult with severe *idiopathic acquired hemolytic* anemia were treated with corticotropin by Gardner and associates [3] In each instance, they observed a diminution in the rate of red cell destruction and a decrease in immunologic abnormalities One patient who had transfusion reactions was transfused with safety as the result of treatment The authors emphasize the value of this form of therapy in the preparation of patients for splenectomy They mention in an addendum that 5 additional patients with idiopathic acquired hemolytic anemia were also benefited by corticotropin therapy Ley and Gardner [4] treated 3 patients with acquired hemolytic anemia with cortisone and obtained results similar to those which had been secured with corticotropin The red cell hemoglobin and hematocrit values gradually rose the reticulocyte counts subsided and the serum bilirubin values returned to more normal levels The Coombs' test titers became weaker or negative In the one patient who demonstrated both osmotic and mechanical fragilities of the erythrocytes these abnormalities disappeared

The case of a 63 year old woman who was said to have idiopathic acquired hemolytic anemia of 24 years known duration was reported by Crary and Beck [25] The disease was of cyclic type and when seen by the authors the patient was in severe hemolytic crisis *With corticotropin and later with* cortisone therapy an almost complete remission of the process was obtained Relapse occurred when the daily cortisone dosage was reduced to 25 mg but improvement followed rapidly when the dosage was increased to 50 mg Seven months later she was observed in partial relapse with a hemoglobin of 8 0 Gm per 100 cc of blood the dosage of cortisone was increased to 75 mg daily In spite of the larger dose hemolysis continued and the dose of cortisone was *raised to 100 mg daily* with little evidence of enhanced therapeutic effect Eleven months after starting therapy she died apparently as the result of bronchopneumonia and cardiac decompensation This case illustrates the fact that some patients with chronic acquired hemolytic anemia become increasingly resistant to cortisone therapy *and demonstrates the* hazards of continued high dosage administration with respect to fluid retention and increased susceptibility to infection

Meyers and [illegible] reported [illegible] patients with [illegible] in whom [illegible] of these [illegible] patients a [illegible] woman [illegible] had [illegible] been [illegible] two years [illegible] been [illegible] three years. [illegible] the patient [illegible] the [illegible] Fig. [illegible] patient [illegible] responded when [illegible] Two of the [illegible]

Fig. [illegible] [illegible] (From [illegible] Meyers, [illegible] and [illegible].)

[illegible] (Figures [illegible] and 6) [illegible] prior to [illegible] of these patients. One of the [illegible] members of the series, a [illegible] woman [illegible] failed to respond to [illegible] a dose of 150 [illegible] and responded only partially [illegible] 200 mg. daily [illegible] with temporary improvement, and the patient has [illegible] been maintained [illegible] two years on [illegible] a dose of 40 [illegible] mg. daily (Figure 7). It is of [illegible] the [illegible] generally falls as [illegible] decreases in response to [illegible] therapy. [illegible] was true in this patient, who [illegible] a marked rise in the [illegible] of an [illegible] at a time when [illegible] and [illegible] evident. The series reported by Meyers and [illegible] has now been extended to include 12 cases, and a summary of the therapy employed and the response [illegible] will be presented [illegible].

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anemia Two patients went into remission after treatment with transfusions and cortisone, which was given in doses of 100 to 200 mg daily Both of these patients had the cold hemagglutinin variety of acquired hemolytic anemia Significant improvement was noted in the remaining 6 patients This was characterized by increase in red blood cell count diminution in reticulocytosis decrease in jaundice regression of the enlarged spleen and decrease of antibody titers However, when it became obvious that remissions could only be maintained by continuous cortisone therapy, splenectomy was done In contrast to the situation seen in previous years these patients were in excellent clinical condition at the time of operation Five of the patients required cortisone for varying periods postoperatively In 3 of these it was ultimately possible to discontinue the medication Two patients required continuous therapy after splenectomy In addition to these cases of idiopathic acquired hemolytic anemia cortisone was employed successfully by Sacks and associates in several patients with symptomatic hemolytic anemia complicating chronic lymphocytic leukemia

In a case of acquired hemolytic anemia in a 76-year old man Hansen and Anderson[17] obtained serial electrophoretic serum protein tracings before during and after treatment with corticotropin Prior to therapy the values were within normal limits although the Coombs test was positive During corticotropin administration which was moderately effective in controlling hemolysis, there was an unusual elevation of the gamma globulins and simultaneously the Coombs' test became negative Immediately after cessation of treatment the Coombs test again became positive and the gamma globulins decreased to normal levels

The experiences of the writer and his associates in the treatment of idiopathic acquired hemolytic anemia with cortisone or corticotropin are sum

Table 84

CLINICAL RESPONSES TO CORTISONE AND CORTICOTROPIN IN TWELVE CASES OF IDIOPATHIC ACQUIRED HEMOLYTIC ANEMIA

Nature of Response	*Number of Patients*	*Subsequent Course*	*Number of Patients*
Complete	[illegible]	Sustained remission of 36 months	1
		Relapse and death	1
		Relapse re treatment and splenectomy with control	5
Incomplete	4	Splenectomy with remission	1
		Splenectomy followed by relapse	2
		No follow up	1
None	1	Splenectomy with partial control	1

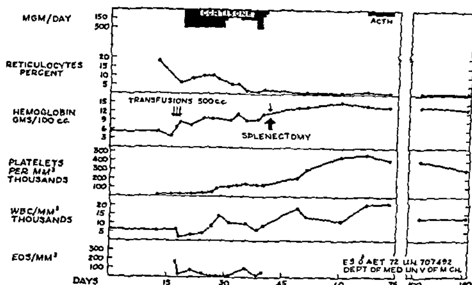


Fig 50 Partial remission induced by cortisone in a 72 year old man with acute hemolytic anemia and thrombocytopenic purpura The risk of splenectomy was thereby reduced Corticotropin was given postoperatively because of signs of hypoadrenalism Remission after splenectomy has been sustained

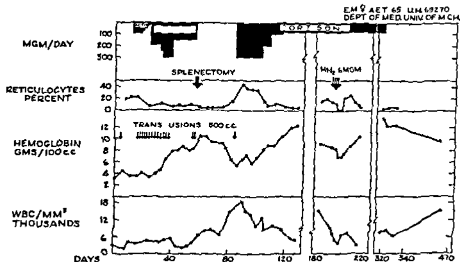


Fig 51 Partial response to cortisone in a 65 year-old woman with exceedingly severe hemolytic anemia of three months duration Splenectomy produced little or no beneficial effect Nitrogen mustard (HN_2) administration depressed bone marrow activity but failed to influence hemolysis Periodic cortisone therapy has maintained the patient in reasonably good health for longer than two years (From Meyers Miller Linman and Bethell [13])

The relatively benign course and high incidence of spontaneous remissions in patients with hemolytic anemia who demonstrate high titers of cold agglutinins in contradistinction to those with warm agglutinins has been emphasized by Sacks, Jahn and Workman [26] Cortisone or corticotropin was employed in 8 patients in the authors series of 19 cases of acquired hemolytic

may be exceedingly difficult, and diagnostic studies always should include careful examination of the bone marrow. Hypoplastic and aplastic anemias, leukemia, and other malignancies will be considered separately, and attention now will be directed toward those disorders in which the disability so far as the blood is concerned is attributable entirely to the lack of neutrophils.

Agranulocytosis

In this acute disorder of granulopoiesis, which is almost always caused by a drug reaction, the usual outcome is either death in a relatively short time or spontaneous recovery after withdrawal of the responsible agent and treatment with antibiotics. It is therefore difficult to evaluate the results of therapy directed toward the neutropenia itself. Nevertheless, evidence is quite conclusive that cortisone or corticotropin may either hasten recovery from agranulocytosis or prove to be actually lifesaving in severely ill patients with profound neutropenia.

A case of agranulocytosis due to prolonged use of sulfadiazine, sulfamerazine, and sulfamethazine in which cortisone administration was followed by prompt and rapid recovery was reported by Caldwell and associates.[9] Although slight improvement in the blood picture was noted at the time cortisone therapy was begun, the patient's condition was still considered grave, and the dramatic change in status is presumably attributable to the cortisone. An even more convincing report of the successful use of corticotropin in a case of agranulocytosis was published by McMillin.[31] The patient, a healthy 36-year-old deep-sea diver, suffered complete paraplegia as the result of an accident. He developed cystitis and later pneumonia and was treated with sulfadiazine, since sensitivity to penicillin precluded its use. Sulfadiazine was given for seven days in a dose of 1.0 Gm. three times daily for treatment of the cystitis and was subsequently increased to 1.0 Gm. every four hours when signs of pneumonia appeared. His symptoms and fever gradually subsided over a period of seven days and the medication was discontinued. He then developed rapidly progressive leukopenia until his leukocyte count reached a level of 450 per cu. mm. with complete absence of neutrophils. He was extremely ill, with high fever, cyanosis, and gallop rhythm, and his death appeared imminent. A sternal marrow examination showed lack of granulocyte development beyond the progranulocyte stage. Administration of corticotropin in doses of 25 mg. every six hours for three days and subsequently in reduced dosage for an additional four days was followed by a prompt and dramatic rise of the leukocyte values to a maximum in excess of 70,000 per cu. mm. Many immature granulocytic elements were present. The marrow exhibited a marked change with evidence of active neutrophilic differentiation. Clinical improvement was noted within the first 24 hours of corticotropin administration and progressed satisfactorily. Later the peripheral blood and marrow findings became normal.

Two patients with agranulocytosis following the use of thiosemicarbazone for rheumatoid arthritis were treated with corticotropin by Virk-

marized in Tables 34 and 35. Of 12 patients 7 had complete clinical and hematologic remissions but in only 1 of these was the response sustained after discontinuing treatment. Partial remissions were obtained in 4 patients and 1 patient, a man aged 45 with severe hemolytic anemia, failed to respond either to corticotropin in a daily dose of 100 units or to cortisone in increasing doses up to 400 mg daily. During the period of cortisone administration the hemoglobin declined to 3.2 Gm. per 100 cc. of blood in spite of daily transfusions of 500 cc.; this was accompanied by increasing jaundice and progressive hepatomegaly and splenomegaly. When resuspended red cells from 4,500 cc. of blood were given over a period of three days together with cortisone, 400 mg. each day, the hemoglobin rose to 10.4 Gm. and splenectomy was performed. The immediate result was favorable and so far the hemolytic process appears to have been largely arrested (see Table 34). A somewhat similar case of acquired hemolytic anemia which appeared to be uninfluenced by corticotropin administration has been reported by Clearkin.[8]

Table 35

DOSE AND DURATION OF INITIAL PERIOD OF HORMONAL THERAPY IN IDIOPATHIC ACQUIRED HEMOLYTIC ANEMIA

Hormone	*Daily Dose*	*Duration of Therapy (days)*
Cortisone	200–400 mg.	19–28
Corticotropin	100–160 units	11–36

The dosage of cortisone during the initial period of treatment was usually 300 mg. by mouth daily, but in some cases 400 mg. was given. The medication was administered in fractional doses every six hours when the oral route was employed. In those few patients who were treated intramuscularly with cortisone the same doses were used as in the case of oral administration but the medication was given in two divided doses twelve hours apart. Corticotropin was given intramuscularly every six hours in doses totaling 100 to 160 units daily. The duration of therapy was longer in patients with acquired hemolytic anemia than in the idiopathic thrombocytopenic purpura group and in most cases exceeded three weeks.

Leukopenic Conditions

Profound diminution in the number of circulating neutrophils with the accompanying hazard of uncontrollable infection occurs in acute agranulocytosis, primary and secondary splenic cytopenias and "periodic neutropenia" as well as in disorders affecting the myelopoietic system as a whole, such as aplastic anemia, leukemia and primary and secondary neoplasms affecting the marrow. Differential diagnosis in these groups of conditions

treatment of splenic neutropenia is scanty The writer has published his observations on 2 cases of Felty s syndrome[11] and another case has since been treated All 3 patients were middle-aged women with long standing rheumatoid arthritis splenomegaly leukopenia and a history of recurring infections In 2 cases administration of corticotropin 25 units every six hours was followed by attainment of normal neutrophil values in 6 and 11 days respectively Relapse promptly followed discontinuance of therapy but second remissions were obtained with cortisone in doses of 100 to 200 mg daily The third patient showed a delayed and incomplete response to corticotropin in doses up to 150 units daily for a period of 17 days When treatment was changed to cortisone 300 mg daily the neutrophil percentage rose from 25 to 93 in seven days whereas the total leukocyte count increased from 1 050 to only 1 500 per cu mm in this period of time After 18 days of cortisone therapy 300 mg daily the leukocyte count was 3 450 per cu mm with 93 per cent neutrophils Although relapse has invariably followed cessation of steroid therapy in Felty s syndrome it has been possible to maintain normal or nearly normal neutrophil values for many months on maintenance cortisone therapy in daily doses of 75 to 100 mg

The correction of neutropenia by cortisone or corticotropin treatment in Felty s syndrome may be attributable to the beneficial effect of the hormones upon the underlying rheumatoid arthritis since it has been shown that the anemia of rheumatoid arthritis is favorably influenced by such therapy [18] On the other hand 2 of the 3 patients discussed above had relatively minor and apparently inactive joint disease and their erythrocyte and hemoglobin values were normal Moreover cortisone or corticotropin administration was accompanied by definite diminution of spleen size It has also been observed that splenectomy may be followed by correction of neutropenia without beneficial effect upon the symptoms and signs of arthritis Therefore, it seems probable that the action of cortisone or corticotropin on the granulocytic equilibrium in Felty s syndrome is largely if not completely independent of their modifying influence on the inflammatory changes of rheumatoid arthritis

The writer has observed a case of apparent primary splenic neutropenia in a 21 year-old woman in whom an excellent hematologic response was obtained during the administration of corticotropin 25 units every six hours The total leukocyte count rose from 1 350 cells per cu mm with 8 per cent neutrophils to 15 050 cells with 79 per cent neutrophils after seven days of therapy Splenectomy was done during the hormone-induced response and there has been no evidence of relapse for a period of five months during which she has received no therapy On the other hand another patient a woman aged 47, suffering with splenic neutropenia which was known to be of at least one year's duration had no granulocytic response whatever to the daily administration of 300 mg of cortisone for a two-week period Splenectomy has been followed by a restoration of normal leukocyte values but it is too early to evaluate the long range effect of the removal of the spleen A similar instance of complete lack of response to corticotropin in a 61 year old

kunen.[31] One of the patients, a woman aged 50, was extremely ill with pneumonia and appeared to be comatose when corticotropin therapy was instituted. Within 18 hours after three injections of 20 mg. of corticotropin, she showed dramatic improvement with return of temperature to normal and rise in leukocyte count. Both of these patients made complete recoveries. In the same article the author reports on the successful use of cortisone in one case and of corticotropin in a second case of thrombocytopenic purpura following the administration of gold salts.

The introduction of phenylbutazone, a compound closely related chemically to aminopyrine, for the treatment of rheumatoid arthritis, gout and other painful inflammatory conditions has been followed by reports of a few instances of agranulocytosis.[32-35] None of the cases so far reported has proved fatal. Cortisone or corticotropin was employed in the treatment of most cases, but the results are, on the whole, difficult to evaluate because for the most part the patients were not severely ill and their management was complicated by the simultaneous use of a variety of therapeutic measures. An exception to these equivocal results may be provided by the case reported by Stifel and Burnheimer.[34] Their patient, a 52-year old woman suffering with rheumatoid arthritis, was given phenylbutazone 200 mg. three times daily for six weeks. She developed complete absence of granulocytes in the peripheral blood, which persisted for five days and was accompanied by intense pharyngitis. There was a dramatic clinical and hematologic response following the administration of corticotropin.

Experience has shown that the presence of infection is no contraindication to the use of cortisone or corticotropin in the management of acute agranulocytosis. On the contrary, the administration of one of these agents together with antibiotics may serve to suppress a dangerous inflammatory reaction and at the same time aid in restoring the defense resources of the body.

Splenic Neutropenia

Severe granulocytopenia as a manifestation of hypersplenism is observed most often in association with rheumatoid arthritis as a component of Felty's syndrome or as an "idiopathic" disorder to which the term primary splenic neutropenia has been given. Hypersplenic leukopenia is usually persistent and relatively stable and is almost never of extreme degree nor associated with the profound marrow alterations which characterize acute agranulocytosis. Nevertheless, patients with splenic neutropenia are especially susceptible to such infections as recurring pneumonitis, and they may fail to respond to antibiotic therapy. Splenectomy is the treatment of choice in such circumstances, but it is not always successful. Moreover, in the presence of an active infection surgery may be contraindicated and, in any event, medical measures which may counteract the process responsible for the leukopenia, however transiently, should prove useful in enhancing defense against infection or in preparation for surgery.

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man with primary splenic neutropenia has been reported by Wintrobe and associates [37]

Periodic Neutropenia

The interesting condition to which Reimann and de Barardinis[38] have assigned the name periodic (cyclic) neutropenia, is characterized by regularly recurring severe neutropenia usually in three week cycles Fever, malaise and inflammation of the mouth and throat with superficial ulcerations of the oral mucosa are common accompaniments of the neutropenia but the cycles may recur without any clinical manifestations The etiology is unknown although because of a similarity to the menstrual cycle an endocrinologic basis has been proposed The occurrence of the condition in both sexes and over a wide range of ages together with the absence of demonstrable hormonal disturbances, renders such an explanation unlikely

A case of periodic neutropenia in a 78 year old man who was treated with corticotropin has been reported by Monto and associates [39] Although this is the oldest patient with periodic neutropenia on record, the diagnosis seems to be established on sound criteria During one of the episodes of neutropenia the patient developed a severe rectal infection followed by pneumonia The leukocyte count remained for three days between 500 and 600 cells per cu mm with almost complete absence of granulocytes and his condition was considered critical The administration of corticotropin 20 units every four hours was followed within a few hours by remarkable clinical improvement The leukocyte count rose to 4 000 per cu mm with 65 per cent neutrophils Because of the abrupt improvement in the clinical and hematologic condition of the patient following corticotropin administration the authors attribute the change to a therapeutic response rather than to a cyclic recovery phase

On the other hand in the case reported by Reimann and de Barardinis [38] administration of a single dose of 25 units of corticotropin during a neutropenic episode was followed by a further decrease in the level of circulating granulocytes whereas the same test dose given during an interval between episodes of neutropenia induced the usual neutrophilic response

Although the question is still unsettled it seems probable that neither cortisone nor corticotropin will have much influence on periodic neutropenia except that in the presence of severe infection the inflammatory reaction may be favorably modified and the degree of neutrophilic response enhanced during the cyclic recovery phase

Neoplasms of the Hemic and Lymphatic Systems

In this category are included the leukemias plasmocytic myeloma and the malignant lymphomas especially Hodgkin s disease follicle lymphoma lymphocytic sarcoma and reticulum cell sarcoma Whether or not all of these conditions may ultimately be classified as neoplasms is open to question Nevertheless whatever the provocative factor may be in a specific condition or in an individual case and however the clinical course and pathologic

manifestations may vary the common attribute of the ailments is a progressive disorderliness of growth and differentiation of a more or less specialized mesenchymal tissue Since adrenal steroid therapy or adrenocortical stimulation may modify in a spectacular manner the growth propensities of mesenchymal tissue the administration of 11 oxysteroids or corticotropin to patients with leukemia or lymphoma has aroused a great deal of justifiable scientific interest and unfortunately a considerable amount of unwarranted and futile optimism

Leukemia

Discussion of a particular form of therapy in leukemia requires separate consideration in terms of the primary cellular type of the disorder the degree of nondifferentiation of the predominant cells (immaturity) in bone marrow lymph tissue and blood the extent of excessive proliferation the severity of associated anemia and thrombocytopenia the age of the patient the clinical manifestations and the duration of the illness Expressed in specific nomenclature [40] the leukemias may be designated according to cellular type as lymphocytic granulocytic monocytic plasmocytic and megakaryocytic They may be categorized as acute subacute or chronic depending upon the degree of differentiation of the proliferative cells and the clinical manifestations and they may be further subdivided into leukemic subleukemic or aleukemic forms which may undergo reversible transition from one to the other according to the number of circulating leukemic cells in the peripheral blood

Within recent years a number of chemotherapeutic agents have been found to be effective in the treatment of some forms of leukemia These include the nitrogen mustards and similarly acting compounds urethane and certain antimetabolites such as the folic acid antagonists and 6 mercaptopurine Undoubtedly more compounds of a like nature will be added to the list of antileukemia agents since none of those now available offers more than limited and temporary benefit All these substances however they may differ in their biochemical reactions owe their action to a suppression of cell growth with a more or less selective effect upon leukemic tissue True remission following their use characterized by complete or partial return to a hematologically normal state as contrasted with mere suppression of cell proliferation must be attributed to the creation of favorable conditions for at least temporary restoration of the hemic equilibrium This concept of the basis for the beneficial effect in leukemia of chemotherapeutic agents as well as that of ionizing radiation implies the persistence in varying degree of a regulatory mechanism of blood cell production and differentiation

From the standpoint of pathologic physiology the effect of cortisone or corticotropin in leukemia is of especial interest because these materials are not primarily destructive or suppressive agents affecting all rapidly growing cells but they exert a selective action on the growth and development of particular cell lines arising from the myeloid and lymphoid reticulum Thus improvement accompanying their use in a case of acute leukemia may be

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Periodic Neutropenia

The interesting condition to which Reimann and de Barardinis[38] have assigned the name periodic (cyclic) neutropenia, is characterized by regularly recurring severe neutropenia, usually in three-week cycles Fever, malaise and inflammation of the mouth and throat with superficial ulcerations of the oral mucosa are common accompaniments of the neutropenia but the cycles may recur without any clinical manifestations The etiology is unknown although because of a similarity to the menstrual cycle an endocrinologic basis has been proposed The occurrence of the condition in both sexes and over a wide range of ages together with the absence of demonstrable hormonal disturbances renders such an explanation unlikely

A case of periodic neutropenia in a 78 year old man who was treated with corticotropin has been reported by Monto and associates[39] Although this is the oldest patient with periodic neutropenia on record, the diagnosis seems to be established on sound criteria During one of the episodes of neutropenia the patient developed a severe rectal infection followed by pneumonia The leukocyte count remained for three days between 500 and 600 cells per cu mm with almost complete absence of granulocytes and his condition was considered critical The administration of corticotropin 20 units every four hours was followed within a few hours by remarkable clinical improvement The leukocyte count rose to 4 000 per cu mm with 65 per cent neutrophils Because of the abrupt improvement in the clinical and hematologic condition of the patient following corticotropin administration the authors attribute the change to a therapeutic response rather than to a cyclic recovery phase"

On the other hand in the case reported by Reimann and de Barardinis[38] administration of a single dose of 25 units of corticotropin during a neutropenic episode was followed by a further decrease in the level of circulating granulocytes whereas the same test dose given during an interval between episodes of neutropenia induced the usual neutrophilic response

Although the question is still unsettled it seems probable that neither cortisone nor corticotropin will have much influence on periodic neutropenia except that in the presence of severe infection the inflammatory reaction may be favorably modified and the degree of neutrophilic response enhanced during the cyclic recovery phase

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Eventually all patients with acute leukemia become resistant to the form of therapy which they have been receiving. This problem was studied by Kingsley Pillers et al [54] who observed that either the hormones or folic acid antagonists were effective in producing further remissions in approximately 50 per cent of patients showing resistance to one type of therapy.

Chronic Leukemia In the management of chronic leukemia there is little place for the use of cortisone or corticotropin. An exception to this general rule may be made in selected cases of advanced chronic lymphocytic leukemia particularly when it is accompanied by severe anemia or cutaneous manifestations [55] In such cases distinct symptomatic relief may be produced with continued cortisone administration in daily doses of 50 to 75 mg and intervals between blood transfusions may be lengthened.

Hodgkin s Disease and Lymphosarcoma

Patients with advanced Hodgkin s disease may be temporarily benefited by cortisone administration and the terminal phase of the illness rendered more tolerable. The improvement is largely subjective but subsidence of fever relief of pruritus regression of tumor masses and considerable weight gain may occur. Hematologic values may improve and patients who had been considered no longer suitable for nitrogen mustard or triethylene melamine therapy may again be treated with these agents. Moreover the administration of cortisone prior to and during a course of nitrogen mustard therapy tends to diminish markedly the gastric disturbances associated with the latter. As reported by Straus and associates [56] the administration of cortisone as sole therapy in rapidly progressive Hodgkin s disease is not as efficacious as nitrogen mustard or X irradiation. These authors[57] performed serial bone marrow examinations during administration of cortisone to 6 patients with active progressive Hodgkin s disease. The most conspicuous changes were proliferation of erythrocytic granulocytic eosinophilic and megakaryocytic elements as well as reticulum cells associated in some instances with morphologic abnormalities. The development of giant cells of the Sternberg Reed type was noted in the marrow of 3 patients. The authors interpreted this finding as evidence that cortisone does not beneficially affect an important underlying mesenchymal disturbance in Hodgkin s disease.

In disseminated lymphosarcoma the same indications for and limitations of cortisone therapy apply as in advanced chronic lymphocytic leukemia and Hodgkin s disease. Improvement in appetite and sense of well being with some temporary regression of tumor masses constitute justification for the use of hormonal therapy in those patients who are approaching the terminal phase of their illness.

Multiple Myeloma

Reported experience with the use of cortisone or corticotropin in plasmocytic myeloma is somewhat conflicting. Engle and Barr[58] observed no satisfactory response in 3 patients who were treated with corticotropin. In the

attributed to a direct influence on normal regulatory mechanisms—an activation of defense forces such as may sometimes follow an acute infection—rather than to a directly destructive action on leukemic cells Nevertheless regression of lymphoid tumors or fall in the level of circulating leukemic cells induced by cortisone or corticotropin therapy is accompanied by greatly increased uric acid excretion and other biochemical evidences of mass dissolution of neoplastic cells [41-43]

Acute Leukemia Since the first reports of the use of cortisone and corticotropin in the treatment of leukemia appeared in 1950 [42 44-47] the number of publications on the subject has grown to include data on many hundreds of patients In spite of the voluminous literature the experience and conclusions of the writers may be summarized quite briefly Much of the following material is adapted from papers and discussion presented at the Second Clinical ACTH Conference [48-52]

In acute leukemia administration of cortisone or corticotropin will lead to decided clinical and hematologic improvement in from 40 to 80 per cent of cases treated In a smaller number approximately 20 per cent remissions will be virtually complete The difference in reported incidence of improvement is caused largely by the age of the patients duration of the disease when treated and criteria of therapeutic evaluation Best results are obtained in children Young adults may respond favorably but older persons with acute leukemia are rarely benefited by hormonal therapy and in some instances an adverse effect may be produced The prospect for improvement appears to be better in the acute lymphocytic than in the acute granulocytic variety of leukemia but the writer has observed excellent temporary results in cases of the latter type On the other hand there appears to be general agreement that the acute monocytic form is not responsive to cortisone or corticotropin therapy

If treatment is discontinued after a good result has been obtained relapse will usually occur within a period of two to ten weeks On the other hand continued therapy with cortisone may serve to maintain remission for six months or longer Second remissions occur in about one-half of the patients who initially obtained favorable results whereas a third remission is rarely observed

Although cortisone and corticotropin produce fewer undesirable effects—at least in the early period of their administration—than do the folic acid antagonists the latter type of therapy when successful will effect longer and more evenly maintained remissions than can be secured with the hormones For this reason many clinicians advocate the combined use of cortisone or corticotropin and Aminopterin or Amethopterin during the early stages of therapy If remission is obtained the hormonal therapy is stopped and the antagonist is continued Marie and associates[53] have used the following plan of therapy with reported success in acute leukemia of children Treatment is instituted with Aminopterin 1 mg daily and cortisone 25 to 100 mg daily Once the remission is obtained Aminopterin 2 to 3 mg weekly and cortisone 12 5 mg daily are given

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writer's reported series of 8 cases[59, 60] treated with either cortisone or corticotropin, excellent temporary improvement was noted in 4. In 3 the response was slight, and in 1 it was considered equivocal. This series has now been increased to 12 with approximately the same proportionate results. The main evidences of a favorable response are relief of bone pain, increase in sense of well being, and improvement in laboratory values, including decrease in the number of plasmoblasts and proplasmocytes in the marrow, lowering of serum globulin and blood nonprotein nitrogen values and sometimes increase in hemoglobin.

In suitable cases urethane is the treatment of choice in plasmocytic myeloma. Cortisone or corticotropin should be reserved for use in patients who refuse to take urethane or are not benefited by it, as well as in those who are suffering with intense and disabling pain.

In concluding the section on the use of cortisone and corticotropin in the management of neoplasms of the hemic and lymphatic systems, it is fitting to quote from Farber's[61] summarization of the reports and discussion on this subject:

The steroid hormones, chemical compounds which are carcinolytic, and any new form of therapy which may be developed, should be used as part of the total care given the patient with disseminated cancer. Until the day has come when actually curative agents will be at hand, it must be remembered that the steroid hormones and chemical substances now used in the treatment of acute leukemia, lymphosarcoma, Hodgkin's disease, and other forms of disseminated cancer cannot be administered as the sole form of therapy to a patient with disseminated cancer. Antibiotics, transfusions, general supportive measures, and great attention to the emotional and social aspects of the problem are but part of the burden of the doctor who cares for such patients. Therefore ACTH and cortisone in themselves give no answers to the doctor who is confronted with the patient with incurable cancer. To those groups of workers who have assumed the responsibility of giving total care particularly to patients with leukemia and the lymphomas, including Hodgkin's disease, ACTH and cortisone come as a welcome addition to the tools which may be used in behalf of these patients. To the investigator in the field of cancer, the steroid hormones offer new challenges in the fundamental questions concerning their nature, mode of action, and their potentialities, which remain to be answered.

Hypoplastic Anemia and Refractory Anemia

The hypoplastic anemias vary in severity from almost complete absence of myeloid blood cell precursors, with resulting granulocytopenia and extreme thrombocytopenia, as well as aregenerative anemia, to relatively mild forms characterized by diminished red cell production. In the former group all forms of therapy, including use of the hormones, are generally unavailing, although cortisone or corticotropin may temporarily control hemorrhagic manifestations. In less severe degrees of hypoplastic anemia, hormonal therapy may have a decided myelostimulatory effect in chronic idiopathic forms of the disease; the frequency of transfusions may be lessened by continued maintenance therapy with cortisone or by its periodic administration.

Favorable results following corticotropin administration to 4 patients with so called refractory anemia have been reported by Hill and Hunter.[6] In one of these patients, a woman aged 53 years with chronic mild erythro-

cytic hypoplasia the effect of the hormone in stimulating red cell production appears to be clear cut In the other 3 improvement may well have been spontaneous Loeb[63] has observed diminished need for blood transfusions in 2 adults with chronic hypoplastic anemia following institution of cortisone or corticotropin therapy Shulman[64] observed no benefit from the use of either cortisone or corticotropin in 8 of 10 patients suffering with various types of refractory anemia In 4 of the 10 patients significant reticulocytosis occurred during the administration of corticotropin but in only 2 of these was there an associated rise in the hematocrit In but 1 of these 2 patients was the erythrocytic response reproducible

Three patients suffering with aplastic anemia were treated with hormonal therapy by Wintrobe and associates[37] Two of these patients improved subjectively and diminution of purpura was observed No change took place in the volume of packed red cells or in the number of reticulocytes

In aplastic anemia attributable to drug intoxication such as that which may follow chloramphenicol administration the use of cortisone or corticotropin has proved completely ineffective in the writer's experience with 6 cases so treated It must therefore be concluded that the hormones have a limited field of usefulness in the hypoplastic and refractory anemias and that they are most likely to prove beneficial in the chronic relatively mild forms of aregenerative anemia

Other Hematologic Conditions in Which Adrenocortical Therapy May Prove Useful

Allergic Purpura

The Schonlein Henoch form of vascular purpura characterized by petechiae ecchymoses abdominal pain bloody stools and often hematuria has been shown to respond to corticotropin by Stefanini and associates[6] and by Wooley[66] Cortisone has been employed successfully by Kugelmass[6] in this type of purpura Relapse tends to occur after discontinuing therapy but hormonal treatment is indicated during acute exacerbations of the illness in order to lessen the risk of acute abdominal emergencies or progressive renal damage

Thrombotic Thrombocytopenic Purpura

Two patients suffering with this disseminated disease of arterioles characterized by widespread deposition of hyalin thrombi in the walls of terminal vessels were observed by Meacham and associates[83] Administration of corticotropin to one of the patients appeared to have a beneficial effect Although this disorder is almost if not altogether uniformly fatal intensive hormonal therapy appears to be indicated as the only available means except possibly splenectomy of modifying its progressive course

Sickle Cell Anemia

A single case report by Sass[69] offers quite convincing evidence of the effectiveness of cortisone and corticotropin in ameliorating the symptoms

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of crisis in a patient with sickle cell anemia The author concludes that although the hormones do not appear to elevate significantly the erythrocyte or hemoglobin values, they in some manner tend to prevent the vascular occlusions which are characteristic of the crises of this disease

Disseminated Neoplasms Other than Those of the Hemic and Lymphatic Systems

Cortisone and corticotropin have a restricted but definite role in the therapy of disseminated neoplasms other than those of blood cell forming and lymphatic tissues Judicious use of hormonal therapy in terminal states can modify the clinical course by lessening pain, improving appetite and restoring a degree of well being Such application of adrenocortical therapy constitutes treatment of the patient instead of the specific disease

Nathanson and Kelley[70] have reviewed the indications for the use of cortisone and corticotropin in neoplastic diseases From the collective evidence it seems clear that these hormones are ineffective in a wide variety of carcinomas and in neoplasms of connective tissue origin

With the exception of 1 patient suffering with mycosis fungoides which probably should be classed with the malignant lymphomas, Taylor and Morris[71] observed no effect upon tumor growth in their patients with advanced neoplasms These included 2 cases of carcinoma of the breast with metastases 1 of carcinoma of the trachea and 1 of Ewing s tumor

Spies and associates[7] observed lessening of pain and ' increased comfort in 3 patients with inoperable squamous cell carcinoma There was no objective evidence of improvement

Farber and colleagues[73] observed no effect upon the primary disease following administration of cortisone or corticotropin in 4 cases of neuroblastoma with metastases 1 of Wilms s tumor with metastases, 1 of osteogenic sarcoma with metastases, 1 of angiosarcoma 1 of undifferentiated sarcoma 1 of reticulum cell sarcoma and 1 of transitional cell sarcoma Eliel[74] has reported similar negative results of hormonal therapy in a wide variety of carcinomas and sarcomas other than those of lymphocytic origin Taylor[75] observed augmentation of tumor growth in 3 of 4 patients with advanced carcinoma of the breast who were treated with corticotropin In 1 patient with carcinoma of the trachea administration of corticotropin resulted in improvement of the airway due to decreased swelling around the tumor and relief of bronchial spasm The tumor progressed and biopsies showed no change

In some cases of prostatic and mammary carcinoma however, the results with cortisone have been more encouraging In 4 of 5 patients with recurrent prostatic carcinoma treated with cortisone to induce adrenal atrophy Hayward[76] reported favorable response consisting of return of appetite increased strength and vigor and diminished pain manifested by lessened narcotic requirement Evidence is accumulating[77–79] to show that adrenalectomy followed by maintenance therapy with cortisone in some cases of mammary

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Disseminated Neoplasms Other than Those of the Hemic and Lymphatic Systems

Cortisone and corticotropin have a restricted but definite role in the therapy of disseminated neoplasms other than those of blood cell forming and lymphatic tissues. Judicious use of hormonal therapy in terminal states can modify the clinical course by lessening pain, improving appetite and restoring a degree of well being. Such application of adrenocortical therapy constitutes treatment of the patient instead of the specific disease.

Nathanson and Kelley[70] have reviewed the indications for the use of cortisone and corticotropin in neoplastic diseases. From the collective evidence it seems clear that these hormones are ineffective in a wide variety of carcinomas and in neoplasms of connective tissue origin.

With the exception of 1 patient suffering with mycosis fungoides, which probably should be classed with the malignant lymphomas, Taylor and Morris[71] observed no effect upon tumor growth in their patients with advanced neoplasms. These included 2 cases of carcinoma of the breast with metastases, 1 of carcinoma of the trachea, and 1 of Ewing's tumor.

Spies and associates[7] observed lessening of pain and "increased comfort" in 3 patients with inoperable squamous cell carcinoma. There was no objective evidence of improvement.

Farber and colleagues[73] observed no effect upon the primary disease following administration of cortisone or corticotropin in 4 cases of neuroblastoma with metastases, 1 of Wilms's tumor with metastases, 1 of osteogenic sarcoma with metastases, 1 of angiosarcoma, 1 of undifferentiated sarcoma, 1 of reticulum cell sarcoma and 1 of transitional cell sarcoma. Ehel[74] has reported similar negative results of hormonal therapy in a wide variety of carcinomas and sarcomas other than those of lymphocytic origin. Taylor[75] observed augmentation of tumor growth in 3 of 4 patients with advanced carcinoma of the breast who were treated with corticotropin. In 1 patient with carcinoma of the trachea, administration of corticotropin resulted in improvement of the airway due to decreased swelling around the tumor and relief of bronchial spasm. The tumor progressed and biopsies showed no change.

In some cases of prostatic and mammary carcinoma, however, the results with cortisone have been more encouraging. In 4 of 5 patients with recurrent prostatic carcinoma treated with cortisone to induce adrenal atrophy, Hayward[76] reported favorable response consisting of return of appetite, increased strength and vigor, and diminished pain manifested by lessened narcotic requirement. Evidence is accumulating[77-79] to show that adrenalectomy followed by maintenance therapy with cortisone in some cases of mammary

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14

Diseases of the Kidney

John A Luetscher Jr

A limited number of patients with disease of the kidneys can be helped substantially by the administration of cortisone The selection and management of such patients as well as the use of cortisone in other conditions complicated by renal disease require the recognition of certain unique problems Cortisone affects the mass of material presented to the kidneys for excretion the renal capacity for excretion and the selective reabsorption or rejection of specific substances Cortisone may modify the clinical and chemical signs of renal disease The following discussion will present some fundamental concepts which should be useful in determining the treatment of patients with diseased kidneys References to the basic contributions described in the following paragraphs can be found in a recent review [1]

In Addison s disease the failure of sodium conservation and of potassium elimination by the kidneys can be remedied by the administration of desoxycorticosterone (DCA) This steroid alone however fails to return renal function entirely to normal The low rate of glomerular filtration and of renal plasma flow and the failure of water diuresis in Addison s disease can be improved by the administration of cortisone or the closely related substance hydrocortisone

The effects of large doses of cortisone upon renal function in the normal man are in some respects exaggerations of the useful effects in adrenocortical deficiency Cortisone in dosage of 100 mg or more per day leads to an elevation of the glomerular filtration rate and of the renal plasma flow above the normal level The effects upon sodium balance are not consistent probably because both filtration and reabsorption of sodium are enhanced to a variable extent by the administration of cortisone In general the larger the dose the more sodium is likely to be retained Potassium may be lost from

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already present After more prolonged administration both the effects upon proteinuria and edema may be reversed and an improvement in these signs may become evident Patients with renal disease frequently show an elevation in blood pressure when cortisone is administered There is a general impression that the increase in blood pressure on administration of cortisone is not as frequent or as great as that which follows the administration of corticotropin The blood pressure usually falls to pretreatment levels within one to five days after medication is withdrawn

The effects of adrenocortical therapy upon excretory function of the kidneys depend upon the status of renal function and the reversibility of any deficiency of excretion due to disease Patients with normal renal function may show a supranormal glomerular filtration rate renal plasma flow and excretion of other substances when cortisone or corticotropin is administered Patients with moderate reduction of renal function due to disease may or may not manifest improvement when these hormones are administered In certain instances of the nephrotic syndrome striking increases of renal function have been observed Other patients may show very little improvement of renal function under the influence of cortisone

If the renal injury is of such limited reversibility that a significant increase in excretory function does not occur azotemia or potassium intoxication may appear under the influence of the increased catabolic effects of cortisone or corticotropin The accumulation of urea and other products of protein catabolism may lead to uremia or a rapid increase in the serum potassium level may reflect the inability of the kidney to handle an increased load [24]

In patients with advanced renal failure the effect of cortisone upon uremia or upon potassium intoxication is variable from case to case In some instances a dangerous aggravation of the signs of renal insufficiency may take place In others renal function is stimulated so that a balance may be struck or there may even be a reduction in the level of blood waste In any case no additional potassium should be given to such patients and it is probably advisable for them to be placed on a relatively low protein intake pending determination of the effects of cortisone upon the renal function The blood urea and serum potassium should be followed carefully at such times since significant changes may occur from day to day

In addition to the direct effects of cortisone upon the human kidney it is possible that there may be modifications in endogenous adrenal secretion modifications which may affect the pattern of the disease and of its symptoms In the nephrotic syndrome for example there is an excess of sodium retaining activity in the urinary corticoids during the edematous stage The abnormal level of sodium retaining activity is reduced when effective diuresis follows the administration of cortisone Such a modification in the spectrum of active adrenocortical hormones suggests that the modification of the clinical picture may sometimes be influenced by the substitution of cortisone for another hormone

To summarize the clinical importance of these observations, we must

the cells and excreted by the normal kidneys, with some reduction in the serum potassium concentration (In the absence of effective renal function however the potassium level of the serum may rise during the administration of cortisone) Polyuria may become manifest after some days of cortisone administration Renal glycosuria has been noted even when the blood sugar has not risen to abnormal levels There are increases in the rates of excretion of urates amino acids and several other substances during cortisone treatment

The effects of cortisone upon several types of experimental nephritis in animals deserve consideration because of a certain parallelism with human disease Either cortisone or corticotropin will prevent the lesion of anaphylactic glomerulonephritis which occurs in animals injected with foreign serum protein The protection given to the kidneys is manifested even though antibodies are formed and apparently react with the antigen at the usual time with a reduction in the serum complement levels In contrast with this beneficial result the administration of cortisone or of corticotropin to animals whose kidneys have been injured by nephrotoxic serum does not result in a correction of the lesion Although the pathologic lesion may be modified the net effect upon the animal is not clearly beneficial and indeed some of the evidences of the nephrotoxic nephritis may be aggravated The adrenocortical hormones may produce edema and hypertension especially in the presence of renal disease Several types of experimental proteinuria have been shown to be aggravated by cortisone and other adrenal hormones

When very large doses of adrenocortical steroids or corticotropin are given to experimental animals renal lesions may be observed DCA can produce a deposition of hyaline or fibrinoid material in the walls of the arterioles and the renal glomeruli and can lead to a fatal nephrosclerosis if high dosage is prolonged Cortisone can prevent the vascular lesions of overdosage of DCA in other organs but the renal lesions are not affected Excessive doses of cortisone or corticotropin produce a capillary dilatation in the glomeruli with hyperemia and escape of protein and blood into the renal tubules Examination of the kidneys of patients who have received large doses of cortisone or corticotropin prior to death has shown only rare lesions of this type Bilateral cortical necrosis of the kidneys has been described in animals treated with cortisone when the Shwartzman phenomenon was evoked Fortunately no comparable situation has been observed in man

The effect of cortisone upon the course of the forms and stages of renal disease in man is highly variable as might be expected from the differences of response in experimental animals There is no conclusive evidence that adrenocortical therapy can cure any disease of the kidneys but in the most favorable cases remissions of long duration may be established Certain clinical and chemical signs of renal disease may be modified Just as in experimental animals many patients show increased proteinuria when cortisone is administered The sodium retaining effect of these hormones may result in the accumulation of edema especially in cases in which edema is

minemia respond as well as those with less striking changes Edema is a problem only because it may increase during treatment if the respiratory reserve is small paracentesis of the pleural cavity and of the peritoneum may be advisable in order to relieve the extreme distention Patients with marked reduction of renal function or with very poor output of urine are more liable to develop difficulties during treatment Hence every effort should be made to establish a good urine output before beginning cortisone therapy Anemia of a severe grade reflects a reduction in red cell mass which may be an impediment to elimination of fluid in certain cases If the anemia is severe (hematocrit below 30 per cent) it is quite justifiable to transfuse the patient before treatment with cortisone is begun Significant elevation of the blood pressure may reflect active glomerulonephritis or a severe reduction in renal function but in many instances it offers no serious barrier to treatment especially when cortisone is used

In many instances it is not possible to determine with any accuracy before treatment whether glomerulonephritis is responsible for the nephrotic syndrome When significant hematuria elevation of the blood pressure and marked reduction of renal function are present the diagnosis of glomerulonephritis is more probable Nevertheless moderate degrees of hematuria and reduced renal function are frequently present without clear cut signs of glomerulonephritis and such patients may recover entirely without residual changes A sharp differentiation between those cases of nephrotic syndrome resulting from glomerulonephritis and those of unknown etiology does not seem feasible in many instances and has little weight in the outcome of a single course of treatment

The effects of cortisone upon patients with the nephrotic syndrome may be divided into three general stages The initial stage lasting approximately five days is characterized by a fall in urine volume reduction in urine sodium output and an increase in body weight as edema increases The reduction in urine flow is not entirely dependent upon the sodium retention since it occurs even in patients who have very little sodium in the urine before treatment and in those whose intake of sodium is restricted In the latter group the serum sodium concentration may be decreased during this stage of oliguria There may be a sharp rise in serum potassium at this time accompanied by an increase in blood urea With the increasing volume of body fluids respiratory difficulty may ensue if the reserve is reduced by a tense accumulation of fluid in the abdominal and pleural cavities Proteinuria tends to increase at this time especially if the initial rate of protein excretion was not very high The total serum protein may be reduced in concentration

After some days of cortisone administration—usually at the end of about five days—gradual improvement in urine volume is noted Proteinuria when it is increased tends to return nearer to the control level An improvement in the serum protein and albumin concentration may be noted The body weight tends to fall slightly during this stage as edema is reduced The serum sodium concentration returns toward normal and a small amount

recognize that renal function is under the control of hormones of the same type as cortisone and that the excretory function of the kidneys is stimulated by the administration of cortisone The ability of the diseased kidney to respond to such stimulus is variable however and the disadvantages of an increased load placed on the kidney by the catabolic effects of cortisone may exceed the benefit of a limited increase in function A separation of these components may sometimes be made by comparing the level of serum creatinine with the levels of serum urea and potassium The creatinine, since it is produced at a steady rate will give a rough index of renal function independent of the load the serum urea and potassium will reflect the kidneys ability to cope with the increased catabolic load and will tend to rise out of proportion to the change in the serum creatinine when the kidneys are unable to cope with increased demands [4]

Under the influence of cortisone, the patient with renal disease may manifest increased proteinuria edema and hypertension but in general these are reversible phenomena which will disappear when dosage is reduced or administration of the drug is stopped Other complications of cortisone therapy may occur in patients with renal disease about as frequently as in other patients It seems unlikely that any permanent renal lesion will be observed in man following the administration of cortisone although lesions have been noted in the kidneys of animals given excessive doses of several adrenocortical steroids Some of the specific complications of certain phases of renal disease will be discussed in this chapter under the appropriate headings

Treatment of the Nephrotic Syndrome

The most impressive results obtained with cortisone in the treatment of renal disease have been observed in those cases of the nephrotic syndrome due to unknown causes or to glomerulonephritis [3-7] Less satisfactory results have been obtained with the nephrotic manifestations of disseminated lupus erythematosus and the Kimmelstiel Wilson syndrome These latter conditions will be discussed subsequently under specific headings

The nephrotic syndrome is characteristically manifested by heavy proteinuria hypoalbuminemia increased serum globulin greatly increased sedimentation rate (E S R) hypercholesteremia and increase in the serum fat Edema is usually an important manifestation although it is variable in extent *Renal function is generally well preserved* but in a few instances marked reduction in renal excretory function is observed The urine output varies but frequently is subnormal In patients with reduced function and oliguria the levels of blood urea and serum potassium may be elevated and there may be marked acidosis Some degree of anemia is frequently observed Elevation of the blood pressure with retinopathy and cardiac enlargement or failure is seen in some cases associated with glomerulonephritis

In the selection of cases and preparation for treatment with cortisone little importance need be attached to the severity of the cardinal clinical manifestations Patients with massive proteinuria and severe hypoalbu

following steps A good urine output should be established before treatment by forcing fluids especially if there is any evidence of nitrogen retention or elevation of the serum potassium The sodium intake should not be so strictly controlled during the first days of treatment as to aggravate the tendency to hypotonicity Patients seem to do better on diets permitting 1 0 to 2 5 Gm of sodium chloride per day than on those containing a lower content of sodium An excess of sodium chloride at this time may simply result in a very rapid accumulation of edema During the later days of treatment or afterward diuresis may be accompanied by a loss of potassium which may result in a lowered serum level During the stage of diuresis the potassium level should be checked and supplementary potassium (3 to 5 Gm per day as potassium chloride) may be given to prevent further depletion Much larger quantities of potassium may occasionally be necessary in order to control the tendency to hypokalemia during a profuse diuresis while the patient is receiving cortisone When a diuresis follows discontinuance of cortisone therapy a significant fall in blood pressure may occur and this may be associated with symptoms of weakness general muscular aching and postural hypotension A pronounced sinus tachycardia may be observed at this time especially in children In most instances no specific therapy is necessary but we have occasionally used concentrated human serum albumin or blood to increase the blood volume If it is suspected that frank adrenal insufficiency may be present after a long course of cortisone therapy a small replacement dose of cortisone or DCA might be used namely 25 mg of cortisone or 5 mg of DCA daily for a few days

A very serious complication of treatment may be related to the tendency of the nephrotic patient to develop infection which may be obscured by the effect of adrenocortical therapy upon the clinical appearance of the infection A hospitalized patient with the nephrotic syndrome who is receiving cortisone has a better than even chance of developing a clinically significant infection during or immediately after his course of therapy Recognition of such a problem presents unusual difficulties Fever is unusual in patients receiving large doses of cortisone while the leukocyte count is characteristically elevated in patients with nephrosis who are receiving cortisone The only manifestation of a severe generalized infection may be restlessness inability to eat or the appearance of some local signs Even with the greatest watchfulness some patients will develop signs of a severe infection immediately upon withdrawal of the drug In addition to the consequences of the infection itself such an event frequently interrupts or prevents improvement in renal function Because of these difficulties and dangers associated with infection during treatment the patient should receive full doses of an effective broad spectrum antibiotic Even under these conditions vigilance must not be relaxed since infection may occur

In addition to these specific complications of therapy in the patient with nephrosis any of the other possible complications of treatment with cortisone may occur and appropriate safeguards should be set up to detect and treat them as promptly as possible

of sodium may appear in the urine If cortisone administration is continued for more than 10 days a gradual increase in diuresis may ensue and a considerable amount of edema may be eliminated The proteinuria may diminish at this time When diuresis occurs while adrenocortical therapy is being given the potassium concentration of the serum may fall below the normal level and for this reason the level of the serum potassium should be followed carefully

When the administration of cortisone is stopped release of sodium and of water usually ensues This process may continue until elimination of edema is complete but in a number of instances the diuresis is not sufficient to be clinically useful During diuresis the mass of protein excreted per day frequently is reduced and in a few individuals complete cessation of proteinuria occurs At this time the abnormalities of the urinary sediment such as casts fat filled epithelial cells and increased numbers of red blood cells may be reduced in number or disappear entirely When diuresis and reduction in proteinuria occur a substantial rise in the serum protein and albumin levels usually follows

In those patients who are fortunate enough to obtain complete elimination of edema and proteinuria a remission may be expected to last from some weeks to an indefinite period In a few fortunate patients all the signs of the nephrotic syndrome disappear entirely and the patient may have no further trouble the serum proteins and fats gradually return to normal levels and the E S R approaches normal over a period of some months Such a remission may be interrupted at any time by an infection or stress of any sort or without obvious cause for the relapse Continuation of proteinuria or of urinary sediment abnormality is apparently not compatible with prolonged remission

Whether or not the course of treatment is followed by diuresis or improvement in proteinuria some improvement of renal excretory function frequently is obtained In the most favorable cases the level of glomerular filtration rate may be strikingly increased but in other instances the defect in filtration is apparently not so easily reversed and only a minor increase in filtration rate is noted These observations have raised the hope that the progressive diminution in renal function which is the most destructive aspect of the disease might in certain instances be delayed or prevented

Complications

A number of complications of nephrosis as a result of adrenocortical therapy have been noted In most instances they may be prevented or controlled by appropriate management but in certain instances administration of the hormones may have to be terminated These problems will be considered in the order of their occurrence During the first days of cortisone administration the syndrome of increasing edema low serum sodium concentration, and high serum potassium concentration may be associated with the oliguria There does not appear to be any simple satisfactory way to meet this combination of problems but they may be minimized by the

hormone is during its administration Many patients show a sharp increase in glomerular filtration rate during the administration of cortisone but apparently the sodium retaining action of the hormone prevents the release of appreciable quantities of sodium during treatment The improvement in renal function continues for some time after treatment is terminated while sodium reabsorption diminishes when the cortisone is withdrawn In such individuals a diuresis would naturally be expected to ensue It is much more difficult to explain the changes in proteinuria and in the activity of the renal lesion as judged by the urinary sediment Such changes may appear during or after treatment with cortisone or corticotropin

Since cortisone and corticotropin have apparently opposite effects on over all adrenal secretory activity it is difficult to explain the results either in terms of an increase or a decrease in adrenal function It has already been mentioned that there is some evidence in favor of the hypothesis that abnormalities of adrenal secretion may have an unfavorable influence on the course of glomerulonephritis or of the nephrotic syndrome [4] The relationship of possible endogenous changes in adrenal function to the observed modification of the nephrotic syndrome will require much additional study From a practical standpoint however an important conclusion may be drawn in patients with the nephrotic syndrome there is no objection to abrupt withdrawal of cortisone therapy because the release of fluid associated with temporary adrenal insufficiency may be an important factor in the production of favorable results For this reason we have not usually tapered the dose of cortisone but rather have given full dosage up to the last day of the planned course of treatment and then have withdrawn the drug entirely After brief courses of treatment the development of signs of adrenal insufficiency great enough to affect the patient adversely has been seen only very rarely

Although treatment with cortisone for 10 to 14 days is followed by complete and lasting remission in some cases recurrence of the nephrotic picture frequently occurs within a few months In other patients unsatisfactory or limited improvement is seen Such patients may be benefited by repeated or continuous therapy

If the initial trial of cortisone is not followed by a satisfactory response additional courses of larger dosage may be beneficial Further treatment is also indicated when recurrence of symptoms and signs occurs after temporary improvement This plan of treatment results in persistent remission in at least 40 per cent of the children and adults so treated [7]

The frequency of relapse and progression of the disease to a fatal termination after isolated brief courses of adrenocortical therapy has suggested the use of more continuous therapy for the period of three to six months after initial treatment when recurrence is most common [7] It seems undesirable to subject these patients to the risks of continuous high dose therapy Administration of cortisone 100 to 400 mg on three days of each week appears to avoid many of the hazards and undesired effects while giving a considerable degree of protection against recurrence [8]

Comparison of the Effects of the Adrenocortical Hormones

The results just described may be induced not only by cortisone but also by the closely related compound, hydrocortisone, and by corticotropin A number of questions concerning selection of the hormonal agent to be used, dosage and duration of treatment remain unanswered even though considerable information has been collected Many of the original observations on the treatment of the nephrotic syndrome were made during administration of corticotropin whereas cortisone was used in less effective dosage and for briefer periods of time The results of these studies appeared to indicate a superiority of performance of corticotropin in inducing diuresis and in improving renal function When the drugs are studied under more equitable conditions there does not seem to be a conspicuous difference in the therapeutic results obtained Apparently, several differences in the general type of response can be expected The use of corticotropin may be followed by a more pronounced antidiuresis during the early days of treatment Diuresis may occur during the first or second week of treatment with corticotropin with cortisone it is more likely to be seen during the third week Effective elimination of edema may not occur during the administration of either agent but a favorable result may follow cessation of therapy Treatment with corticotropin generally produces a somewhat greater elevation of blood pressure and reduction of cholesterol concentration in certain patients In contrast cortisone and hydrocortisone are effective when given by mouth It may be advantangeous to avoid multiple injections in certain cases of the nephrotic syndrome such as those affecting children or very edematous patients or when unusual susceptibility to infection and the reduced defense against infection during hormonal therapy make parenteral administration hazardous

Dosage and Duration of Treatment

Dosage and the duration of treatment must be determined for each individual and much remains to be learned about the advantages of different plans of administration A dosage lower than 100 mg per day of cortisone or of hydrocortisone is probably relatively ineffectual Similarly a course of less than 10 days of treatment at this dosage level probably yields only a small proportion of good results A recommended starting point might be a course of 10 to 12 days of treatment with 200 mg of cortisone per day If the cortisone is given as a saline suspension of microcrystals intramuscularly the effect is delayed several days Oral administration appears to give an equally satisfactory response Although children appear to require approximately the same dose as adults we have not usually given more than 200 mg per day to small children, but have given 300 or 400 mg per day to adults in certain resistant cases There may be some advantage in continuing the administration of cortisone for as long as three weeks The effects of long term treatment are still being explored [5, 6]

It is important to remember in connection with the use of cortisone in such patients that improvement is as likely to occur on withdrawing the

agent is extremely difficult. The effects of cortisone upon the clinical signs and laboratory evidences of the disease have been variable.[7,8] Hematuria has usually continued in spite of administration of the hormone. In certain instances of gross hematuria there has been a reduction in the intensity of bleeding, but in other instances increases in hematuria have been noted during prolonged treatment with cortisone or after its cessation. Edema tends to increase during the period of hormonal treatment and to diminish immediately afterward. Elevation of blood pressure has been noted when adrenocortical therapy has been administered; this effect has been more striking with corticotropin than with cortisone. Cardiac failure would offer a contraindication to the use of cortisone. In the rare instances of oliguria or anuria, cortisone and corticotropin have been tried with variable effects. Use of these agents in the anuric patient is dangerous, since a rapid increase in uremia and potassium intoxication may appear during such treatment. Although long term study may demonstrate some special circumstances in which the use of the adrenocortical preparations may be of value in acute nephritis, at present it does not seem justifiable to use these agents except in carefully selected cases in which the outlook appears extremely poor.

Latent Glomerulonephritis. Latent glomerulonephritis is a stage of the disease in which no clinical manifestations are obvious while the urinary signs continue. There is no evidence that the use of cortisone at this stage affects significantly the course of the disease.[7] If proteinuria becomes heavy, edema appears, the serum proteins fall, and the cholesterol rises—all indications of the approach of the nephrotic syndrome—it may be justifiable to use cortisone in an effort to modify the development of this stage of the disease.

Chronic Glomerulonephritis. Chronic glomerulonephritis usually progresses with or without clinical manifestations or flare-ups to a stage of terminal renal insufficiency with uremia and hypertension. Although some of these patients respond to adrenocortical therapy with improved renal function, the gain is usually temporary. Other patients show no such reversibility of the impairment of excretory function and react to cortisone only with a rise in the level of the blood urea and a comparable clinical deterioration. In general, the use of cortisone at this stage is hazardous and there is no concrete evidence that its use will be followed by clinical improvement.[3]

Renal Lesions of Disseminated Lupus Erythematosus and Polyarteritis. Disseminated lupus erythematosus and polyarteritis (periarteritis nodosa) may affect the kidneys and produce manifestations closely resembling those of the various stages of glomerulonephritis. Unfortunately, the renal lesions seem to respond much less favorably to adrenocortical therapy than do the general lesions of this disease. The evidences of renal injury appear to be relatively unaltered by the administration of cortisone, although certain specific manifestations may be improved. For example, the development of the nephrotic syndrome during the course of disseminated lupus erythematosus may be halted in certain instances by the use of cortisone. The effects under these circumstances are similar to those seen in the nephrotic syn-

To summarize these findings in the nephrotic syndrome the mode of action of cortisone has not been ascertained although several favorable results of its administration have been described Treatment of these patients requires special attention to certain problems concerned with the impairment of renal function, in addition to the more usual complications of therapy Although the most suitable plan of administration has not been settled cortisone is usually given in courses of two to three weeks duration in full dosage this is followed by abrupt cessation of therapy to take advantage of the possible rebound effect upon adrenocortical function In about half of the patients so treated a temporary remission will occur during which the patient will be free from edema and possibly from proteinuria and changes of the urinary sediment In a few instances complete and lasting remission of the disease is established at this time, but in many recurrence of edema may follow a respiratory infection or other stress Such recurrences may be treated like the original attack More continuous therapy is indicated if only temporary relief is obtained after brief courses of treatment

When effective diuresis fails to follow within a week after termination of treatment it is highly unlikely that further improvement attributable to the cortisone will ensue The patient may sometimes be relieved of edema by administration of concentrated human serum albumin (20 to 50 Gm per day for four to seven days) or by paracentesis and the use of Southey s tubes After a rest period a second course of hormonal treatment may be considered

Prognosis

The effect of cortisone upon the long range outlook for the nephrotic syndrome cannot be accurately defined because of the lack of a strictly comparable control series It is clear that the use of effective antibiotics has reduced the high morbidity and mortality associated with infection The prognosis for the adult suffering from the nephrotic syndrome has been further improved by the administration of cortisone [7] The long term benefits of cortisone are less obvious in children in whom the disease follows a *more benign course* The development of more effective plans of treatment holds promise of further improvement in prognosis

Renal Diseases in Which Cortisone Is of Doubtful Value

Glomerulonephritis Since cortisone has been useful in the nephrotic syndrome in which glomerulonephritis may play a role it is quite natural that trial studies should have been made of the effects of cortisone upon other stages of glomerulonephritis In general the results have been disappointing Clinical benefit has only rarely occurred and no substantial evidence of improvement in the urinary sediment or other signs of the disease has been noted

Acute Glomerulonephritis *Acute glomerulonephritis is a disease of* benign outlook and variable course in which evaluation of any *therapeutic*

tients with disease of the kidneys excepting those with advanced renal insufficiency

Cortisone has been shown to be of value in the treatment of the nephrotic syndrome Since certain unusual problems may be encountered the physician should take special precautions as outlined

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drome associated with glomerulonephritis, although the fundamental lesion in the kidney usually is not altered and relapse is almost inevitable after a temporary period of benefit[7] Prolonged treatment of these diseases may stabilize an advancing renal insufficiency in certain cases, but in others the renal lesion progresses inexorably to uremia

Diabetic Nephropathy (Kimmelstiel-Wilson Syndrome) Diabetic nephropathy does not appear to respond favorably to cortisone, even though some of the manifestations resemble those of the nephrotic syndrome[9]

Toxemia of Pregnancy Toxemia of pregnancy with hypertension, edema, proteinuria and some suppression of urine has been treated with cortisone[10] Although temporary improvement has been observed in toxemic patients the benefit is short lived and the use of cortisone in the toxemia of pregnancy must be considered still a highly experimental procedure

Anuria Due to Acute Tubular Necrosis or Injury Anuria due to acute tubular necrosis or injury and occurring after vascular collapse or intoxication does not seem to offer ideal conditions for a trial of cortisone, although its use in this connection has been suggested The principle of conservative management of anuria is to diminish to a minimum catabolism of proteins and release of potassium The effects of cortisone in increasing metabolism and release of potassium would offer a serious contraindication to its use in the anuric patient It is difficult to visualize how adrenocortical therapy could have any beneficial influence in the presence of established tubular injury or necrosis

Uremia This condition is a contraindication to the use of cortisone

Pyelonephritis Pyelonephritis or other infections of the urinary tract should constitute a serious contraindication to the use of cortisone because of the demonstrated effect of cortisone and corticotropin in breaking down the resistance to infection Although the use of an effective antibiotic will usually control infection under such circumstances, the rapid spread of urinary tract infection in patients with Cushing s syndrome and in certain patients with pyelonephritis who have been treated with cortisone should serve as a warning that even full doses of antibiotics may not adequately control an infection in the presence of a high level of circulating corticoids

Summary

The administration of cortisone to patients with renal disease presents certain specific problems

1 The catabolic action of cortisone may increase the amount of urea potassium and other substances to be excreted by the kidneys

2 The increase in renal function which appears in the normal man under the influence of cortisone either may be exaggerated or may fail to appear in the patient with renal disease

3 The proteinuria edema oliguria and hypertension characteristic of many diseases of the kidneys may be temporarily aggravated during cortisone administration

With appropriate precautions cortisone may be administered to pa-

variety of mental symptoms that these patients present Depression of some degree often associated with retardation is perhaps most frequent, or the retardation may be replaced by irritability in the form of agitation, anxiety crying spells or noncooperative behavior Both retardation and irritability may appear in the same patient at different times Variation in the clinical psychiatric picture not only is seen from patient to patient but also occurs conspicuously in the course of the disease in any one patient

The psychiatric picture of Addison s disease is often much like that of Cushing s syndrome [8] This is surprising since the disorders are so different from the physiologic standpoint The asthenia may be sufficiently great to dominate the picture and mask many psychologic symptoms so that they pass unnoticed

Good descriptions of the psychiatric aspects of either the adrenogenital syndrome or the syndrome seen in pheochromocytoma are not commonly found in the literature

Hormonal Therapy in Psychiatric Practice Cortisone corticotropin and thyroid gonadal and other hormones have been tried as therapeutic agents in many forms of mental disturbance [13] The results have been conflicting and the successes few It seems to be easier to cause than to cure psychosis by manipulating hormones Discouragement however should not prevail because of these observations Data are rapidly accumulating that show an undoubted relationship between endocrine glands and brain These data are so significant and illuminate the problem from so many angles that it seems reasonable to hope that in the future much will be learned about the etiology of the schizo-affective group of reactions This is the greatest contemporary problem in psychiatry

Other hormones that might be mentioned are those which either by their lack or by their excess seem to bear a relation to mental disease Many have been given as therapeutic agents and the use of androgens and estrogens has met with some success The hormone most extensively used in the treatment of these diseases is insulin for schizophrenia Early enthusiasm for this therapy has not been justified by a statistical study of results but insulin certainly has a conspicuous if short lived effect upon schizophrenic symptoms in many cases

Psychiatric Effects of the Adrenocortical Hormones in Therapeutic Doses

In the last few years cortisone and corticotropin have been available for therapeutic use and have proved to be of value in the treatment of a wide variety of disorders As a result there has been an opportunity to study the effects of these hormones and related compounds upon behavior It is now clear that the incidence of mental disturbances in patients receiving adrenocortical therapy is higher than would be expected in the general patient population The exact incidence is not easy to determine partly because it is difficult to say whether or not minor behavior changes are related to hormonal therapy and partly because patients are treated by a large number of

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Neuropsychiatric Disorders

Stanley Cobb Gardner C Quarton and Lincoln D Clark

Mental Symptoms of Endocrine Disorders

For a long time evidence has indicated that endocrine disorders are sometimes associated with mental changes The mental symptom of hyper and hypo thyroidism are familiar to most physicians Occasionally in hyperthyroidism the symptoms may be schizophrenic with delusions hallucinations and catatonia The change from the affective to the schizoid picture may be rapid as in Case 14959 reported by Means [1] In contrast to the reduced cerebral metabolism in myxedema [2] it has not been possible to demonstrate altered cerebral metabolism in hyperthyroidism [3]

Mental disturbances following removal of parathyroid tumors have been described by Cope[4] and others [5,6] The patients become extremely apprehensive as the high level of calcium in the blood falls to normal This state of anxiety is promptly relieved by intravenous administration of some form of calcium

Mental disturbances of late pregnancy and the puerperium are probably related to hormonal readjustments These reactions are usually depressive often with strong schizophrenic coloring Fairly typical depressions without schizoid symptoms are common however and short paranoid episodes without obvious depression are known to occur The well known emotional disturbances of the menopause may be thought of as similar phenomena

Cushing's syndrome whether caused by basophilic adenoma of the pituitary or by adrenocortical hyperplasia is often accompanied by severe mental symptoms[7-11] that sometimes may be relieved by operative removal of the adrenal tumor Some cases have shown lesions of the brain and changes in the spinal fluid No single clear cut psychiatric picture emerges from the

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be encountered Serious disturbances of mood are common These range from extreme elation with the other clinical features characteristic of mania to profound depression with severe retardation mutism and stupor Some patients have suicidal tendencies and several suicides have been reported [18,19] The depressed patients frequently talk about their families and may ask that relatives not be permitted to visit them The extreme retardation may make special psychiatric nursing care necessary Sometimes it is hard to maintain adequate nutrition

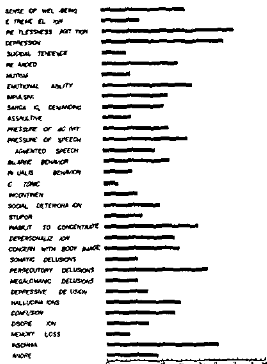


FIG 52 Type and incidence of severe mental disturbances associated with the use of adrenocortical hormones in 34 patients (The most common symptom associated with mild reactions is euphoria)

Suspiciousness and paranoid thinking are common The paranoid ideas are often related to the medical treatment situation Many of these patients have serious medical diseases and as a result have quite intense relationships with their doctors and nurses Also cortisone and corticotropin therapy has been given a magic quality because of its dramatic effectiveness in some cases and because of the rarity of these hormones in the early years Many patients were being treated under experimental conditions with very close observation All of these factors tend to influence the paranoid content of the patient's thought Vivid illusions and hallucinations frequently are intimately concerned with the paranoid ideation

The delusional thinking is almost never well organized or systematized

physicians for many different conditions Glaser[13] has tentatively suggested an incidence of 5 per cent

Mild Reactions

Patients who are only mildly disturbed during hormonal treatment seem to have an exaggeration of the sense of well being (which is almost universal) even to the point of euphoria or hypomanic reaction This is related by some authors to the therapeutic success of the hormones in relieving unpleasant and disliked symptoms of the underlying disease for which therapy was instituted Many cases however, have shown euphoria before any relief of symptoms was apparent In Hollender's[14] well studied case a week of cortisone therapy (100 mg per day) brought on a hypomanic reaction with elation and apprehension but no other symptomatic change The apprehension was explained by the patient as resulting from fear of addiction because the feeling of elation was so pleasant From this case as well as others it would seem that the euphoria develops in spite of adverse psychologic situations indicating that the reaction is produced by pharmacologic action It must be admitted, however that the mechanism of the euphoric effect is not yet known

Patients with slight or transient disturbances may also show depression, restlessness and difficulty in concentrating Some complain of a sense of unreality or depersonalization It is rather common to hear that the patient is dizzy and has a feeling of pressure in the head or unusual tingling sensations that frequently are located over the forehead [15, 16] In more disturbed patients these sensations are not mentioned so often but it may be that they are masked by more dramatic symptoms

Severe Reactions

At the present time a rather large number of cases of obvious mental disturbance associated with cortisone or corticotropin therapy have been studied and reported in the literature although not many are described in detail It is possible to determine with some degree of accuracy whether or not the disturbance has any characteristic features In Figure 52 the symptoms frequently found in these patients are listed Included in the tabulation are cases reported in the literature in adequate detail [13–17] as well as those studied by us Figure 52 cannot be regarded as containing reliable statistical information about the incidence of these symptoms because the data have been collected from several sources and the failure of an author to use a certain word in describing a mental status does not mean that the word could not have been used Furthermore such a tabulation obscures the specific features of individual cases It does give a fair idea however, of the variety and type of symptomatology found in severe mental reactions

Grossly disturbed patients show a variety of symptoms, as revealed in Figure 52 The onset of mental difficulty is often indicated by restlessness excitement emotional lability, or the expression of a paranoid idea Insomnia is an important feature and may suggest that more difficulties will

days after the corticotropin was omitted she suddenly recovered and the unusual mental symptoms did not return The patient had no history of previous mental disorders but had led a rather lonely and unsatisfactory life She had diabetes and arteriosclerotic heart disease but there was no evidence that the diabetes was out of control or that she had sustained an episode of congestive failure coronary occlusion or cerebrovascular thrombosis

Case 2

This 41 year-old woman was admitted to the hospital on January 11 1951 for further treatment of generalized lymphocytic lymphoma The disease had previously responded favorably to a total of 2 565 units of corticotropin given over the course of 30 days There was no past history of psychiatric illness No untoward mental changes had occurred during the first course of treatment On the second admission cortisone was given from March 3 through March 13 in a total dosage of 1 3 Gm

The condition of the patient was psychiatrically uneventful until March 12 At that time she was noted to have marked press of speech and to be highly exhilarated The following day she became suspicious agitated and frightened She maintained that the ward nurse was psychoanalyzing her and used as evidence the fact that the desk lamp at the nurses station was pointed in her direction In addition she stated that the other patients were talking about her and deliberately making noise to upset her Ward conversations became the source of auditory illusions of paranoid depressive quality e g that she was going to be sent to a mental ward She claimed that she was unable to keep track of time and that her memory was defective For the next few days her mental state was variable she was essentially normal at times yet at other times suffered auditory hallucination and expressed paranoid formulations of events going on about her On March 16 the patient entered a state resembling catatonic stupor She became immobile rigid mute and negative The eyelids were held half-closed and a fine tremor was present in the lips eyelids and hands There was resistance to passive movement Unswallowed saliva dripped from her mouth Cerea flexibilitas was demonstrated on several occasions During the next few days this stuporous state continued but it was punctuated by a variety of verbal and motor symptoms Speech returned intermittently but consisted of word salad with punning and echolalia much in evidence For a time her only verbal response to questions or even to rhythmic clapping of the hands was to intone ring rang as if she were a bell At other times posturing grimacing and a curious fixed unblinking stare were observed

The psychosis continued in this variable course On March 22 a state of overactivity panic and assaultiveness developed which reminded some observers of catatonic excitement Reality contact slowly improved however She again verbalized depressive delusions and multiple ideas of reference in regard to the environment Suspiciousness and fear were again evidenced On March 30 1951 the patient suddenly improved she was in good contact and smiled but remained reticent and timid Lucid periods occurred with increasing frequency but in the interim hallucinations poorly structured paranoid delusions and inappropriateness of affect were in evidence It was not until May 13 that the mental state became permanently normal

Subsequent to discharge on May 23 the patient remained quite well for three months Her lymphoma then became worse but responded favorably to X ray therapy She has since remained well from a psychiatric standpoint

Convulsions

Convulsions that sometimes occur during treatment with cortisone and corticotropin[21] are of considerable theoretic interest since desoxycorti

and may change from hour to hour It is often concerned with the patient s own body Sometimes it is possible to follow the development of a somatic delusion Beginning with a vague feeling of depersonalization a patient may then express concern over some part of the body and finally make some bizarre delusional statement It is quite likely that this common clinical feature results from the fact that these patients are suffering from a medical illness and have frequently heard a good deal of talk about their bodies and the possible effects of therapy Sometimes the patient s concern centers on a real bodily change such as a slightly swollen face or minimal hirsutism Salt and water metabolism have even been discussed by patients who link with their delusions what they have obviously overheard the doctors saying

Speech disturbances are related both to the mood disorder and the ideational content It is not unusual to note an extreme pressure of speech Individuals who are usually taciturn may decide to tell the story of their lives In the more disturbed cases speech is disorganized and fragmented One patient adopted a Southern accent

Overt behavior is related both to mood and thought content A few patients become extremely overactive assaultive and combative Some show bizarre and ritualistic movements

Some patients are confused and disoriented and seem to have loss of memory It is not unusual however to find patients with gross delusions and hallucinations who still seem to be perfectly oriented and without any evidence of memory disturbance

In this group of patients it is unwise to attempt to distinguish between organic and functional psychoses or between neurotic and psychotic reactions [6] because we are not able to say what the mechanisms are for the obvious changes in function Furthermore some patients show symptoms of both kinds in separate episodes The following case reports will serve to illustrate this and to demonstrate the rapidly changing clinical picture which is sometimes seen

Case I

A 52 year old single woman was treated with corticotropin 20 units a day intravenously for an exfoliative dermatitis No unusual psychologic symptoms were noted until the third day of therapy when she began to moan cry and refuse food In the afternoon and evening it was difficult to arouse her A review of her drug intake and reports of the nonprotein nitrogen blood sugar and electrolytes did not explain her condition The next day she was profoundly depressed but without delusions disturbing preoccupations or hallucinations She was not confused or disoriented and showed no memory loss Her sudden crying spells amazed her since there was nothing to be depressed about The depression disappeared and corticotropin was continued but on the eighth day of therapy she became talkative and irrational Extremely confused and disoriented she kept saying I don t know where I am—what am I doing here? Corticotropin was omitted and on that day she was distinctly euphoric and complained of dizziness but quickly returned to her usual mental state Three days after corticotropin was discontinued she again became depressed drowsy and apathetic She believed she was dead and said Why do you torture a dead person so? This was followed by a brief period in which she was active and combative but most of the time she was mute and unresponsive Several

days after the corticotropin was omitted she suddenly recovered and the unusual mental symptoms did not return. The patient had no history of previous mental disorders but had led a rather lonely and unsatisfactory life. She had diabetes and arteriosclerotic heart disease but there was no evidence that the diabetes was out of control or that she had sustained an episode of congestive failure, coronary occlusion or cerebrovascular thrombosis.

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The condition of the patient was psychiatrically uneventful until March 12. At that time she was noted to have marked press of speech and to be highly exhilarated. The following day she became suspicious, agitated and frightened. She maintained that the ward nurse was psychoanalyzing her and used as evidence the fact that the desk lamp at the nurse's station was pointed in her direction. In addition she stated that the other patients were talking about her and deliberately making noise to upset her. Ward conversations became the source of auditory illusions of paranoid depressive quality, e.g., that she was going to be sent to a mental ward. She claimed that she was unable to keep track of time and that her memory was defective. For the next few days her mental state was variable: she was essentially normal at times, yet at other times suffered auditory hallucinations and expressed paranoid formulations of events going on about her. On March 16 the patient entered a state resembling catatonic stupor. She became immobile, rigid, mute and negative. The eyelids were held half closed and a fine tremor was present in the lips, eyelids and hands. There was resistance to passive movement. Unswallowed saliva dripped from her mouth. Cerea flexibilitas was demonstrated on several occasions. During the next few days this stuporous state continued but it was punctuated by a variety of verbal and motor symptoms. Speech returned intermittently but consisted of word salad with punning and echolalia much in evidence. For a time her only verbal response to questions or even to rhythmic clapping of the hands was to intone "ring, rang" as if she were a bell. At other times posturing, grimacing and a curious fixed unblinking stare were observed.

The psychosis continued in this variable course. On March 22 a state of overactivity, panic and assaultiveness developed which reminded some observers of catatonic excitement. Reality contact slowly improved, however. She again verbalized depressive delusions and multiple ideas of reference in regard to the environment. Suspiciousness and fear were again evidenced. On March 30, 1951 the patient suddenly improved: she was in good contact and smiled, but remained reticent and timid. Lucid periods occurred with increasing frequency but in the interim hallucinations, poorly structured paranoid delusions and inappropriateness of affect were in evidence. It was not until May 13 that the mental state became permanently normal.

Subsequent to discharge on May 23 the patient remained quite well for three months. Her lymphoma then became worse but responded favorably to X-ray therapy. She has since remained well from a psychiatric standpoint.

Convulsions

Convulsions that sometimes occur during treatment with cortisone and corticotropin[21,2] are of considerable theoretic interest since desoxycorti

costerone (DCA) apparently is effective in preventing seizures Woodbury et al [23,24] have reported that in the rat brain excitability is increased by cortisone and decreased by DCA The electroshock threshold is lowered after cortisone This experimental work suggests that specific mechanisms for the seizures seen in patients may soon be found When seizures occur in patients receiving cortisone or corticotropin however, it is difficult to be sure whether they are caused by the therapy or are related to changes produced by the underlying medical disease Many patients receiving adrenocortical therapy have diseases in which convulsions may occur as a part of the illness, without hormonal therapy Disseminated lupus erythematosus is perhaps the best example There is the possibility that cortisone and corticotropin make seizures more likely in all cases However it has been stated[25] that the presence of fever indicates that the convulsions are secondary to the disease whereas in the absence of fever convulsions are said to be the result of administration of the hormone It is hard to see how this theory can be supported at present since we know so little about the mechanism of action of these hormones

The fact that seizures occur is also of interest because many patients receiving cortisone or corticotropin therapy have abnormal electroencephalograms (EEG) [15, 6–28] The EEG is sometimes abnormal however when there is no mental disturbance No consistent correlation between the EEG and other clinical features has been determined in the patients reported

Duration and Course of Mental Reactions

The duration of mental symptoms which are associated with hormonal therapy varies Many patients will have difficulty only for a day or so In the cases studied by Glaser[13] the longest period during which symptoms persisted was 35 days and in those reported by Clark Bauer and Cobb,[15] it was 150 days All the patients studied so far have recovered excepting those with serious preexisting mental disease and of course those who committed suicide or died from the underlying medical disease There does not appear to be a significant difference in the duration of those disturbances associated with corticotropin and those associated with cortisone

Mental reactions do not seem to have any consistent correlation with the institution duration or cessation of therapy Some patients who were noted to be upset had been under treatment for only two to seven days Others had been receiving treatment without difficulty for over 100 days when the mental disturbance first appeared Cases are reported in which mental symptoms were first noted after hormonal therapy was terminated Furthermore a close relationship has not been conclusively established between the onset of mental symptoms and the sizes of the single dose the average daily dose or the total dosage of cortisone or corticotropin Some patients have developed dramatic symptoms on small doses but in spite of the absence of a clear correlation the incidence of mental disturbance seems to be higher in the series of patients receiving high dosage than in the group treated with small quantities of these hormones

Pathology and Physiology

The incidence of mental disturbances during hormonal therapy is apparently related to the nature of the disease for which the hormones are used Patients with disseminated lupus erythematosus seem to be prone to develop difficulties On the other hand, surprisingly few mental disturbances, other than minimal euphoria,[9] were noted in a series of patients with pemphigus who received large doses of the hormones Present evidence does not explain the dissimilar psychologic reactions occurring during therapy for different diseases This variation may be caused by an increased incidence of underlying brain damage in some conditions or it may be wholly a matter of dosage or duration of treatment[10]

It is of course, tremendously important to decide whether or not there is any physiologic result of therapy that is consistently associated with mental disturbance Up to this time no such association has been found Ransohoff et al[11] have suggested that these mental symptoms are associated with potassium depletion In the largest series of cases reported, however no consistent correlation was found between serum electrolyte changes and mental symptoms[15,17] Schieve Scheinberg and Wilson[22] stated that after two weeks of corticotropin therapy their patients showed a decrease in cerebral blood flow and an increase in cerebral vascular resistance as measured by the nitrous oxide method but they also demonstrated that cerebral oxygen and glucose metabolism were within normal limits Furthermore the findings in 2 of their patients who were psychotic did not differ notably from those in other patients of the group[3] Many physiologic mechanisms might possibly be upset by cortisone or corticotropin therapy and hypotheses concerning some of these have appeared At present considerably more study is indicated

Many patients developing mental symptoms during treatment with cortisone or corticotropin have elevated spinal fluid protein without other spinal fluid changes This may be caused by the underlying disease in each case, but since the spinal fluid protein is frequently elevated in Cushing s syndrome this finding may be noteworthy[7] In the future we may know whether cortisone and corticotropin in some way produce an increased spinal fluid protein If they do not it may be that patients with elevated spinal fluid protein are more likely to develop mental symptoms than those with a normal amount It is possible that the permeability of the blood-brain barrier is related to these problems

Prognosis

At present we are not able to say that there are any definite contraindications to cortisone and corticotropin therapy because of a predisposition to mental disturbance Patients who have had previous serious mental disease seem to develop recurrences of their psychoses in some instances It is reasonable therefore to advise against treatment with these hormones in such cases unless their use is deemed essential and the hazard of psychosis is

costerone (DCA) apparently is effective in preventing seizures Woodbury et al [23, 4] have reported that in the rat brain, excitability is increased by cortisone and decreased by DCA The electroshock threshold is lowered after cortisone This experimental work suggests that specific mechanisms for the seizures seen in patients may soon be found When seizures occur in patients receiving cortisone or corticotropin however, it is difficult to be sure whether they are caused by the therapy or are related to changes produced by the underlying medical disease Many patients receiving adrenocortical therapy have diseases in which convulsions may occur as a part of the illness without hormonal therapy Disseminated lupus erythematosus is perhaps the best example There is the possibility that cortisone and corticotropin make seizures more likely in all cases However it has been stated [5] that the presence of fever indicates that the convulsions are secondary to the disease whereas in the absence of fever convulsions are said to be the result of administration of the hormone It is hard to see how this theory can be supported at present since we know so little about the mechanism of action of these hormones

The fact that seizures occur is also of interest because many patients receiving cortisone or corticotropin therapy have abnormal electroencephalograms (EEG) [15, 6–28] The EEG is sometimes abnormal however when there is no mental disturbance No consistent correlation between the EEG and other clinical features has been determined in the patients reported

Duration and Course of Mental Reactions

The duration of mental symptoms which are associated with hormonal therapy varies Many patients will have difficulty only for a day or so In the cases studied by Glaser[13] the longest period during which symptoms persisted was 35 days and in those reported by Clark Bauer and Cobb [15] it was 150 days All the patients studied so far have recovered excepting those with serious preexisting mental disease and of course those who com mitted suicide or died from the underlying medical disease There does not appear to be a significant difference in the duration of those disturbances associated with corticotropin and those associated with cortisone

Mental reactions do not seem to have any consistent correlation with the institution duration or cessation of therapy Some patients who were noted to be upset had been under treatment for only two to seven days Others had been receiving treatment without difficulty for over 100 days when the mental disturbance first appeared Cases are reported in which mental symptoms were first noted after hormonal therapy was terminated Furthermore a close relationship has not been conclusively established between the onset of mental symptoms and the sizes of the single dose the average daily dose or the total dosage of cortisone or corticotropin Some patients have developed dramatic symptoms on small doses but in spite of the absence of a clear correlation the incidence of mental disturbance seems to be higher in the series of patients receiving high dosage than in the group treated with small quantities of these hormones

Etiologic Theories

The question quite naturally arises whether or not the type of symptoms found in patients with mental disturbances are specifically caused by cortisone and corticotropin It is obvious that in many ways the e patients are similar to certain other mentally ill individuals Some observers believe that the previous personality of the patient entirely determines the symptomatic picture [8] This view does not entirely explain the frequency with which euphoria and restlessness are found In general these episodes are similar to the mental disturbances already described for a variety of endocrine abnormalities

There is another possibility worth considering It may be assumed that if an individual has lived a relatively normal life up to the time of hormonal therapy and is then precipitated into a psychotic illness he will not have available fixed and rigid psychotic patterns so his illness will be characterized by rapid fluctuations by mood change and by apprehension In addition the illness may show a special pattern made likely by the patient s personality In other words these episodes can be compared with acute schizo-affective episodes

The etiologic question cannot be settled at this time We have not yet been able to establish any simple relation between a physiologic event and the mental disturbance Psychologic factors certainly play a role in determining the nature of the disturbance but we cannot be positive that they precipitate the trouble A number of factors psychologic and physiologic may act in varying combinations It is sometimes said that cortisone and corticotropin may precipitate a psychosis because they may remove psychologic defenses by producing rapid improvement in a psychosomatic disease If a patient has used somatic symptoms to handle an emotional problem and these symptoms are dramatically removed he will have to find other ways of dealing with his problems and these new ways may be psychotic It is true that many cases can be found in which the mental disturbance accompanies improvement in the underlying medical disease It is also true that some patients develop a recurrence of the symptoms of the underlying disease soon after recovering from the psychosis However some patients develop mental symptoms although no change occurs in the medical disease

It is possible that the psychologic meaning of certain situations closely associated with cortisone or corticotropin therapy may have profound influence on the patient Situations of this kind might be the success or failure of therapy anticipation of cure from a magic drug ' the intense interest in the patient by the physician the feeling of being a guinea pig or family expectations of an independence on the part of the patient that is greater than is possible or greater than the patient wishes Some of these situations might produce sufficient emotional stress to cause mental disturbance

Cortisone and corticotropin may produce certain physiologic changes which although not directly responsible for mental reactions effect a secondary emotional response which leads to the disturbance For example the

taken into account Of course the personality pattern of an individual determines to a considerable extent the content and perhaps the nature of the psychologic symptoms, but at present we cannot determine which patients will break down mentally Many who develop serious mental disturbances have had no detectable definitely neurotic traits prior to treatment Some patients with a history of emotional problems do not experience difficulty with hormonal therapy Psychologic testing might be effective in determining predisposition to mental disturbance in these patients but it has yet to be tried in a large enough series of cases to be statistically meaningful

Certainly any patient receiving cortisone or corticotropin therapy should be watched closely for signs of early psychologic change Since suicide is the principal risk when a patient becomes depressed or agitated, proper precautions should be taken to prevent this unfortunate outcome Patients who complain of dizziness heavy feelings in the head and paresthesia and those who develop restlessness insomnia and mild ideas of reference should be watched closely

Treatment

Since patients recover from the mental reactions in days or weeks treatment has consisted mostly of careful observation and support It is probably wise to have the patients followed closely by a psychiatrist and to maintain as much continuity of personnel as possible These patients are frequently quite disturbed by transfers from one ward to another but of course this may be necessary for safety A good many patients with severe depression and some with mania have been treated with electroshock therapy (E S T) with good results No clear indications for E S T can be established beyond those which apply to all psychiatric patients

The most difficult decision to be made is whether or not to stop hormonal therapy In most of the cases studied therapy was terminated and the patients ultimately recovered Sometimes therapy has been resumed later with another hormone or with different doses of the same hormone without further trouble Since we know so little about the etiologic factors however we cannot say whether discontinuing therapy is essential or not It certainly seems wise to discontinue it in most cases

Several treatments of the mental disturbance under consideration are directly related to hypotheses concerning etiology For instance it seems wise to try to find hormones that may antagonize the effects of cortisone Both DCA and testosterone have been given trials that have not yet provided enough evidence for evaluation

Most of the patients show a fairly typical pattern of recovery with periods of almost normal behavior followed by further disturbed periods It is not wise to regard the patient s mental difficulties as ended the first time he seems normal to examination

Since the prognosis is good there is no serious difficulty in discussing the mental disturbance with the family particularly if the possibility of such reaction was mentioned before institution of the hormonal therapy

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patient may become frightened of strange bodily sensations such as dizziness, numbness, paresthesia or vasomotor changes It is possible that factors of this kind may be important in the mental symptoms of some endocrine disorders

Numerous theories have been proposed that explain the mental disturbance by some biochemical or tissue changes but the evidence is not yet sufficient for evaluation It has been suggested that cortisone and corticotropin damage nerve cells [33] Mental symptoms have been blamed on the thrombosis of cerebral vessels [34] Suggestions have been made that cerebral glucose metabolism is interfered with in some way It has been claimed that an acetylcholine like substance found in the blood of patients receiving corticotropin is similar to that found in those experiencing severe emotional tension [35] Since cortisone decreases protein anabolism or increases protein catabolism and increases the deamination of amino acids it has been suggested that cerebral protein metabolism is disturbed Sulfhydryl inhibition also has been mentioned as a possible mechanism [36] Certainly it is possible that these hormones by modifying electrolyte and water metabolism may disturb the permeability of nerve cellular membranes even though gross correlations have not been established between mental symptoms and serum electrolyte changes Many steroids produce anesthetic or analgesic effects Some such mechanism might lead to certain psychologic disturbances However cortisone is believed to produce this effect less frequently than do other hormones [37] All of these possibilities are worth further study

From the data available at present we believe the most plausible theory is that the mental disturbance is a result of the action of the hormones on cerebral nerve cells that the reaction is in general schizo affective and that psychologic factors are secondary determining to some extent the severity duration and mental content of the symptoms

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In this index the abbreviation *vs* has been used to indicate the comparative evaluation of two or more preparations Page numbers set in *italics* refer to tabulated material or to illustrations *

*Grateful acknowledgment is made to Mrs Muriel S Nooden for her help in preparing this index—F D W L

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